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(54) Title: IL-17 RECEPTOR (57) Abstract Isolated receptors for IL-17, DNA's encoding such receptors, and pharmaceutical compositions made therefrom, are disclosed. The isolated receptors can be used to regulate an immune response. <div style="text-align: center; margin-top: 100px;"><i>Ref. AH, 09/863,818</i></div>		

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TITLE**IL-17 RECEPTOR****TECHNICAL FIELD OF THE INVENTION**

5 The present invention relates generally to the field of cytokine receptors, and more specifically to cytokine receptor proteins having immunoregulatory activity.

BACKGROUND OF THE INVENTION

 Cytokines are hormone-like molecules that regulate various aspects of an immune or inflammatory response. Cytokines exert their effects by specifically binding receptors
10 present on cells, and transducing a signal to the cells. Rouvier et al. (*J. Immunol.* 150:5445; 1993) reported a novel cDNA which they termed CTLA-8. The putative CTLA8 protein is 57% homologous to the predicted amino acid sequence of an open reading frame (ORF) present in Herpesvirus saimiri (HSV) referred to as HVS13 (Nicholas et al. *Virol.* 179:1 89, 1990; Albrecht et al., *J. Virol.* 66:5047;1992). However, the function, if any of
15 either CTLA-8 or HVS13 was not known, nor was a receptor or binding protein for CTLA-8 or HVS13 known. Thus, prior to the present invention, there was a need in the art to determine the function of CTLA-8 and HVS13, and to identify receptor molecules or binding proteins that play a role in the function of these proteins.

SUMMARY OF THE INVENTION

20 The present invention identifies a novel receptor that binds IL-17 (CTLA-8) and HVS13, a viral homolog of IL-17; DNAs encoding the novel receptor and novel receptor proteins are provided. The receptor is a Type I transmembrane protein; the mouse receptor has 864 amino acid residues, the human receptor has 866 amino acid residues. Soluble
25 forms of the receptor can be prepared and used to regulate immune responses in a therapeutic setting; accordingly, pharmaceutical compositions comprising soluble forms of the novel receptor are also provided. Deleted forms and fusion proteins comprising the novel receptor, and homologs thereof are also disclosed. Also provided are methods of regulating an immune response, and methods of suppressing rejection of grafted organs or
30 tissue. These and other aspects of the present invention will become evident upon reference to the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

35 A soluble IL-17 (CTLA-8) protein and an ORF present in Herpesvirus saimiri (HVS13) were expressed as fusion proteins comprising an immunoglobulin Fc region, and used to screen cells for expression of a receptor for IL-17. T cell thymoma EL4 cells were

found to bind the HVS13/Fc as well as murine CTLA8 (IL-17)/Fc fusion protein. A cDNA library from EL4 cells was prepared and screened for expression of the receptor. The receptor is a Type I transmembrane protein with 864 amino acid residues, which is referred to as IL-17R (CTLA-8R). Various forms of IL-17R were prepared, including IL-17R/Fc protein, a soluble IL-17R which contains the signal peptide and extracellular domain of IL-17R, and a soluble IL-17R/Flag® construct. A human IL-17R was isolated from a human peripheral blood lymphocyte library by cross-species hybridization, and exhibits similarities to the murine IL-17R. Oligonucleotide probes and primers are also disclosed.

10 IL-17, HVS13 and homologous proteins

CTLA-8 refers to a cDNA cloned from an activated T cell hybridoma clone (Rouvier et al., *J. Immunol.* 150:5445; 1993). Northern blot analysis indicated that CTLA-8 transcription was very tissue specific. The CTLA-8 gene was found to map at chromosomal site 1a in mice, and at 2q31 in humans. Although a protein encoded by the CTLA-8 gene was never identified by Rouvier et al, the predicted amino acid sequence of CTLA-8 was found to be 57% homologous to the predicted amino acid sequence of an ORF present in Herpesvirus Saimiri, HVS13. The CTLA-8 protein is referred to herein as Interleukin-17 (IL-17).

The complete nucleotide sequence of the genome of HVS has been reported (Albrecht et al., *J. Virol.* 66:5047; 1992). Additional studies on one of the HVS open reading frames (ORFs), HVS13, are described in Nicholas et al., *Virol.* 179:1 89; 1990. HVS13 is a late gene which is present in the Hind III-G fragment of HVS. Antisera developed against peptides derived from HVS13 are believed to react with a late protein (Nicholas et al., *supra*).

As described USSN 08/462,353, a CIP of USSN 08/410,536, filed March 23, 1995, full length murine CTLA-8 protein and a CTLA-8/Fc fusion protein were expressed, tested, and found to act as a costimulus for the proliferation of T cells. Human IL-17 (CTLA-8) was identified by probing a human T cell library using a DNA fragment derived from degenerate PCR; homologs of IL-17 (CTLA-8) are expected to exist in other species as well. A full length HVS13 protein, as well as an HVS13/Fc fusion protein, were also expressed, and found to act in a similar manner to IL-17 (CTLA-8) protein. Moreover, other species of herpesviruses are also likely to encode proteins homologous to that encoded by HVS13.

35 Proteins and Analogs

The present invention provides isolated IL-17R and homologs thereof having immunoregulatory activity. Such proteins are substantially free of contaminating

endogenous materials and, optionally, without associated native-pattern glycosylation. Derivatives of IL-17R within the scope of the invention also include various structural forms of the primary protein which retain biological activity. Due to the presence of ionizable amino and carboxyl groups, for example, an IL-17R protein may be in the form of acidic or basic salts, or may be in neutral form. Individual amino acid residues may also be modified by oxidation or reduction.

The primary amino acid structure may be modified by forming covalent or aggregative conjugates with other chemical moieties, such as glycosyl groups, lipids, phosphate, acetyl groups and the like, or by creating amino acid sequence mutants. Covalent derivatives are prepared by linking particular functional groups to amino acid side chains or at the N- or C-termini.

Soluble forms of IL-17R are also within the scope of the invention. The nucleotide and predicted amino acid sequence of the murine IL-17R is shown in SEQ ID NOs:1 and 2. Computer analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 31 and 32. Those skilled in the art will recognize that the actual cleavage site may be different than that predicted by computer analysis. Thus, the N-terminal amino acid of the cleaved peptide is expected to be within about five amino acids on either side of the predicted cleavage site. The signal peptide is followed by a 291 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 521 amino acid cytoplasmic tail. Soluble IL-17R comprises the signal peptide and the extracellular domain (residues 1 to 322 of SEQ ID NO:1) or a fragment thereof. Alternatively, a different signal peptide can be substituted for residues 1 through 31 of SEQ ID NO:1.

The nucleotide and predicted amino acid sequence of the human IL-17R is shown in SEQ ID NOs:9 and 10. It shares many features with the murine IL-17 R. Computer analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 27 and 28. Those skilled in the art will recognize that the actual cleavage site may be different than that predicted by computer analysis. Thus, the N-terminal amino acid of the cleaved peptide is expected to be within about five amino acids on either side of the predicted cleavage site. The signal peptide is followed by a 293 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 525 amino acid cytoplasmic tail. Soluble IL-17R comprises the signal peptide and the extracellular domain (residues 1 to 320 of SEQ ID NO:1) or a fragment thereof. Alternatively, a different signal peptide can be substituted for the native signal peptide.

Other derivatives of the IL-17R protein and homologs thereof within the scope of this invention include covalent or aggregative conjugates of the protein or its fragments with other proteins or polypeptides, such as by synthesis in recombinant culture as N-terminal or C-terminal fusions. For example, the conjugated peptide may be a signal (or

leader) polypeptide sequence at the N-terminal region of the protein which co-translationally or post-translationally directs transfer of the protein from its site of synthesis to its site of function inside or outside of the cell membrane or wall (e.g., the yeast α -factor leader).

5 Protein fusions can comprise peptides added to facilitate purification or identification of IL-17R proteins and homologs (e.g., poly-His). The amino acid sequence of the inventive proteins can also be linked to an identification peptide such as that described by Hopp et al., *Bio/Technology* 6:1204 (1988). Such a highly antigenic peptide provides an epitope reversibly bound by a specific monoclonal antibody, enabling rapid
10 assay and facile purification of expressed recombinant protein. The sequence of Hopp et al. is also specifically cleaved by bovine mucosal enterokinase, allowing removal of the peptide from the purified protein. Fusion proteins capped with such peptides may also be resistant to intracellular degradation in *E. coli*.

Fusion proteins further comprise the amino acid sequence of a IL-17R linked to an
15 immunoglobulin Fc region. An exemplary Fc region is a human IgG1 having a nucleotide and amino acid sequence set forth in SEQ ID NO:4. Fragments of an Fc region may also be used, as can Fc muteins such as those described in USSN 08/145,830, filed October 29, 1993. Depending on the portion of the Fc region used, a fusion protein may be expressed as a dimer, through formation of interchain disulfide bonds. If the fusion
20 proteins are made with both heavy and light chains of an antibody, it is possible to form a protein oligomer with as many as four IL-17R regions.

In another embodiment, IL-17R and homologs thereof further comprise an oligomerizing zipper domain. Zipper domains are described in USSN 08/107,353, filed August 13, 1993, the relevant disclosure of which is incorporated by reference herein.
25 Examples of leucine zipper domains are those found in the yeast transcription factor GCN4 and a heat-stable DNA-binding protein found in rat liver (C/EBP; Landschulz et al., *Science* 243:1681, 1989), the nuclear transforming proteins, *fos* and *jun*, which preferentially form a heterodimer (O'Shea et al., *Science* 245:646, 1989; Turner and Tjian, *Science* 243:1689, 1989), and the gene product of the murine proto-oncogene, *c-myc*
30 (Landschulz et al., *Science* 240:1759, 1988). The fusogenic proteins of several different viruses, including paramyxovirus, coronavirus, measles virus and many retroviruses, also possess leucine zipper domains (Buckland and Wild, *Nature* 338:547, 1989; Britton, *Nature* 353:394, 1991; Delwart and Mosialos, *AIDS Research and Human Retroviruses* 6:703, 1990).

35 Derivatives of IL-17R may also be used as immunogens, reagents in *in vitro* assays, or as binding agents for affinity purification procedures. Such derivatives may also be obtained by cross-linking agents, such as M-maleimidobenzoyl succinimide ester and N-

hydroxysuccinimide, at cysteine and lysine residues. The inventive proteins may also be covalently bound through reactive side groups to various insoluble substrates, such as cyanogen bromide-activated, bisoxirane-activated, carbonyldiimidazole-activated or tosyl-activated agarose structures, or by adsorbing to polyolefin surfaces (with or without glutaraldehyde cross-linking). Once bound to a substrate, proteins may be used to selectively bind (for purposes of assay or purification) antibodies raised against the IL-17R or against other proteins which are similar to the IL-17R, as well as other proteins that bind IL-17R or its homologous proteins.

The present invention also includes IL-17R with or without associated native-pattern glycosylation. Proteins expressed in yeast or mammalian expression systems, e.g., COS-7 cells, may be similar or slightly different in molecular weight and glycosylation pattern than the native molecules, depending upon the expression system. Expression of DNAs encoding the inventive proteins in bacteria such as *E. coli* provides non-glycosylated molecules. Functional mutant analogs of IL-17R protein or homologs thereof having inactivated N-glycosylation sites can be produced by oligonucleotide synthesis and ligation or by site-specific mutagenesis techniques. These analog proteins can be produced in a homogeneous, reduced-carbohydrate form in good yield using yeast expression systems. N-glycosylation sites in eukaryotic proteins are characterized by the amino acid triplet Asn-A₁-Z, where A₁ is any amino acid except Pro, and Z is Ser or Thr. In this sequence, asparagine provides a side chain amino group for covalent attachment of carbohydrate. Such a site can be eliminated by substituting another amino acid for Asn or for residue Z, deleting Asn or Z, or inserting a non-Z amino acid between A₁ and Z, or an amino acid other than Asn between Asn and A₁.

IL-17R protein derivatives may also be obtained by mutations of the native IL-17R or its subunits. A IL-17R mutated protein, as referred to herein, is a polypeptide homologous to a IL-17R protein but which has an amino acid sequence different from the native IL-17R because of one or a plurality of deletions, insertions or substitutions. The effect of any mutation made in a DNA encoding a IL-17R peptide may be easily determined by analyzing the ability of the mutated IL-17R peptide to inhibit costimulation of T or B cells by IL-17 (CTLA-8) or homologous proteins, or to bind proteins that specifically bind IL-17R (for example, antibodies or proteins encoded by the CTLA-8 cDNA or the HVS13 ORF). Moreover, activity of IL-17R analogs, muteins or derivatives can be determined by any of the assays methods described herein. Similar mutations may be made in homologs of IL-17R, and tested in a similar manner.

Bioequivalent analogs of the inventive proteins may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine

residues can be deleted or replaced with other amino acids to prevent formation of incorrect intramolecular disulfide bridges upon renaturation. Other approaches to mutagenesis involve modification of adjacent dibasic amino acid residues to enhance expression in yeast systems in which KEX2 protease activity is present.

5 Generally, substitutions should be made conservatively; i.e., the most preferred substitute amino acids are those which do not affect the ability of the inventive proteins to bind their ligands in a manner substantially equivalent to that of native mIL-17R or hIL-17R. Examples of conservative substitutions include substitution of amino acids outside of the binding domain(s), and substitution of amino acids that do not alter the secondary
10 and/or tertiary structure of IL-17R and homologs thereof. Additional examples include substituting one aliphatic residue for another, such as Ile, Val, Leu, or Ala for one another, or substitutions of one polar residue for another, such as between Lys and Arg; Glu and Asp; or Gln and Asn. Other such conservative substitutions, for example, substitutions of entire regions having similar hydrophobicity characteristics, are well known.

15 Similarly, when a deletion or insertion strategy is adopted, the potential effect of the deletion or insertion on biological activity should be considered. Subunits of the inventive proteins may be constructed by deleting terminal or internal residues or sequences. Fragments of IL-17R that bind IL-17 can be readily prepared (for example, by using restriction enzymes to delete portions of the DNA) and tested for their ability to bind IL-17.
20 Additional guidance as to the types of mutations that can be made is provided by a comparison of the sequence of IL-17R to proteins that have similar structures, as well as by performing structural analysis of the inventive proteins.

 Mutations in nucleotide sequences constructed for expression of analog IL-17R (CTLA-8R) must, of course, preserve the reading frame phase of the coding sequences and
25 preferably will not create complementary regions that could hybridize to produce secondary mRNA structures such as loops or hairpins which would adversely affect translation of the receptor mRNA. Although a mutation site may be predetermined, it is not necessary that the nature of the mutation *per se* be predetermined. For example, in order to select for optimum characteristics of mutants at a given site, random mutagenesis may be conducted
30 at the target codon and the expressed mutated viral proteins screened for the desired activity.

 Not all mutations in the nucleotide sequence which encodes a IL-17R protein or homolog thereof will be expressed in the final product, for example, nucleotide substitutions may be made to enhance expression, primarily to avoid secondary structure
35 loops in the transcribed mRNA (see EPA 75,444A, incorporated herein by reference), or to provide codons that are more readily translated by the selected host, e.g., the well-known *E. coli* preference codons for *E. coli* expression.

Mutations can be introduced at particular loci by synthesizing oligonucleotides containing a mutant sequence, flanked by restriction sites enabling ligation to fragments of the native sequence. Following ligation, the resulting reconstructed sequence encodes an analog having the desired amino acid insertion, substitution, or deletion.

5 Alternatively, oligonucleotide-directed site-specific mutagenesis procedures can be employed to provide an altered gene having particular codons altered according to the substitution, deletion, or insertion required. Exemplary methods of making the alterations set forth above are disclosed by Walder et al. (*Gene* 42:133, 1986); Bauer et al. (*Gene* 37:73, 1985); Craik (*BioTechniques*, January 1985, 12-19); Smith et al. (*Genetic*
10 *Engineering: Principles and Methods*, Plenum Press, 1981); and U.S. Patent Nos. 4,518,584 and 4,737,462 disclose suitable techniques, and are incorporated by reference herein.

Due to code degeneracy, there can be considerable variation in nucleotide sequences encoding the same amino acid sequence. Other embodiments include sequences capable of
15 hybridizing under moderately stringent conditions (prewashing solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0) and hybridization conditions of 50°C, 5 X SSC, overnight) to the DNA sequences encoding IL-17R, and other sequences which are degenerate to those which encode the IL-17R. In a preferred embodiment, IL-17R analogs are at least about 70 % identical in amino acid sequence to the amino acid sequence of IL-17R proteins
20 as set forth in SEQ ID NO:1 or SEQ ID NO:9. Similarly, analogs of IL-17R homologs are at least about 70 % identical in amino acid sequence to the amino acid sequence of the native, homologous proteins. In a most preferred embodiment, analogs of IL-17R or homologs thereof are at least about 80 % identical in amino acid sequence to the native form of the inventive proteins.

25 Percent identity may be determined using a computer program, for example, the GAP computer program described by Devereux et al. (*Nucl. Acids Res.* 12:387, 1984) and available from the University of Wisconsin Genetics Computer Group (UWGCG). For fragments derived from the IL-17R protein, the identity is calculated based on that portion of the IL-17R protein that is present in the fragment. Similar methods can be used to
30 analyze homologs of IL-17R.

The ability of IL-17R analogs to bind CTLA-8 can be determined by testing the ability of the analogs to inhibit IL-17 (CTLA-8) -induced T cell proliferation. Alternatively, suitable assays, for example, an enzyme immunoassay or a dot blot, employing CTLA-8 or HSV13 (or a homolog thereof which binds native IL-17R) can be used to assess the ability
35 of IL-17R analogs to bind CTLA-8. Such methods are well known in the art.

The IL-17R proteins and analogs described herein will have numerous uses, including the preparation of pharmaceutical compositions. The inventive proteins will also

be useful in preparing kits that are used to detect IL-17 or IL-17R, for example, in patient specimens. Such kits will also find uses in detecting the interaction of IL-17 and IL-17R, as is necessary when screening for antagonists or mimetics of this interaction (for example, peptides or small molecules that inhibit or mimic, respectively, the interaction). A variety
5 of assay formats are useful in such kits, including (but not limited to) ELISA, dot blot, solid phase binding assays (such as those using a biosensor), rapid format assays and bioassays.

Expression of Recombinant Receptors for IL-17

10 The proteins of the present invention are preferably produced by recombinant DNA methods by inserting a DNA sequence encoding IL-17R protein or a homolog thereof into a recombinant expression vector and expressing the DNA sequence in a recombinant microbial expression system under conditions promoting expression. DNA sequences encoding the proteins provided by this invention can be assembled from cDNA fragments
15 and short oligonucleotide linkers, or from a series of oligonucleotides, to provide a synthetic gene which is capable of being inserted in a recombinant expression vector and expressed in a recombinant transcriptional unit.

Recombinant expression vectors include synthetic or cDNA-derived DNA fragments encoding IL-17R, homologs, or bioequivalent analogs, operably linked to
20 suitable transcriptional or translational regulatory elements derived from mammalian, microbial, viral or insect genes. Such regulatory elements include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences which control the termination of transcription and translation, as described in detail below. The ability to replicate in a host,
25 usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants may additionally be incorporated.

DNA regions are operably linked when they are functionally related to each other. For example, DNA for a signal peptide (secretory leader) is operably linked to DNA for a polypeptide if it is expressed as a precursor which participates in the secretion of the
30 polypeptide; a promoter is operably linked to a coding sequence if it controls the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to permit translation. Generally, operably linked means contiguous and, in the case of secretory leaders, contiguous and in reading frame. DNA sequences encoding IL-17R or homologs which are to be expressed in a microorganism
35 will preferably contain no introns that could prematurely terminate transcription of DNA into mRNA.

Useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and pGEM1 (Promega Biotec, Madison, WI, USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed. *E. coli* is typically transformed using derivatives of pBR322, a plasmid derived from an *E. coli* species (Bolivar et al., *Gene* 2:95, 1977). pBR322 contains genes for ampicillin and tetracycline resistance and thus provides simple means for identifying transformed cells.

Promoters commonly used in recombinant microbial expression vectors include the β -lactamase (penicillinase) and lactose promoter system (Chang et al., *Nature* 275:615, 1978; and Goeddel et al., *Nature* 281:544, 1979), the tryptophan (trp) promoter system (Goeddel et al., *Nucl. Acids Res.* 8:4057, 1980; and EPA 36,776) and tac promoter (Maniatis, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, p. 412, 1982). A particularly useful bacterial expression system employs the phage λ P_L promoter and cI857ts thermolabile repressor. Plasmid vectors available from the American Type Culture Collection which incorporate derivatives of the λ P_L promoter include plasmid pHUB2, resident in *E. coli* strain JMB9 (ATCC 37092) and pPLc28, resident in *E. coli* RR1 (ATCC 53082).

Suitable promoter sequences in yeast vectors include the promoters for metallothionein, 3-phosphoglycerate kinase (Hitzeman et al., *J. Biol. Chem.* 255:2073, 1980) or other glycolytic enzymes (Hess et al., *J. Adv. Enzyme Reg.* 7:149, 1968; and Holland et al., *Biochem.* 17:4900, 1978), such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase. Suitable vectors and promoters for use in yeast expression are further described in R. Hitzeman et al., EPA 73,657.

Preferred yeast vectors can be assembled using DNA sequences from pBR322 for selection and replication in *E. coli* (Amp^r gene and origin of replication) and yeast DNA sequences including a glucose-repressible ADH2 promoter and α -factor secretion leader. The ADH2 promoter has been described by Russell et al. (*J. Biol. Chem.* 258:2674, 1982) and Beier et al. (*Nature* 300:724, 1982). The yeast α -factor leader, which directs secretion of heterologous proteins, can be inserted between the promoter and the structural gene to be expressed. See, e.g., Kurjan et al., *Cell* 30:933, 1982; and Bitter et al., *Proc. Natl. Acad. Sci. USA* 81:5330, 1984. The leader sequence may be modified to contain, near its 3'

end, one or more useful restriction sites to facilitate fusion of the leader sequence to foreign genes.

The transcriptional and translational control sequences in expression vectors to be used in transforming vertebrate cells may be provided by viral sources. For example, commonly used promoters and enhancers are derived from Polyoma, Adenovirus 2, Simian Virus 40 (SV40), and human cytomegalovirus. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early and late promoter, enhancer, splice, and polyadenylation sites may be used to provide the other genetic elements required for expression of a heterologous DNA sequence. The early and late promoters are particularly useful because both are obtained easily from the virus as a fragment which also contains the SV40 viral origin of replication (Fiers et al., *Nature* 273:113, 1978). Smaller or larger SV40 fragments may also be used, provided the approximately 250 bp sequence extending from the *Hind* III site toward the *Bgl* II site located in the viral origin of replication is included. Further, viral genomic promoter, control and/or signal sequences may be utilized, provided such control sequences are compatible with the host cell chosen. Exemplary vectors can be constructed as disclosed by Okayama and Berg (*Mol. Cell. Biol.* 3:280, 1983).

A useful system for stable high level expression of mammalian receptor cDNAs in C127 murine mammary epithelial cells can be constructed substantially as described by Cosman et al. (*Mol. Immunol.* 23:935, 1986). A preferred eukaryotic vector for expression of IL-17R DNA is referred to as pDC406 (McMahan et al., *EMBO J.* 10:2821, 1991), and includes regulatory sequences derived from SV40, human immunodeficiency virus (HIV), and Epstein-Barr virus (EBV). Other preferred vectors include pDC409 and pDC410, which are derived from pDC406. pDC410 was derived from pDC406 by substituting the EBV origin of replication with sequences encoding the SV40 large T antigen. pDC409 differs from pDC406 in that a *Bgl* II restriction site outside of the multiple cloning site has been deleted, making the *Bgl* II site within the multiple cloning site unique.

A useful cell line that allows for episomal replication of expression vectors, such as pDC406 and pDC409, which contain the EBV origin of replication, is CV-1/EBNA (ATCC CRL 10478). The CV-1/EBNA cell line was derived by transfection of the CV-1 cell line with a gene encoding Epstein-Barr virus nuclear antigen-1 (EBNA-1) and constitutively express EBNA-1 driven from human CMV immediate-early enhancer/promoter.

35 Host Cells

Transformed host cells are cells which have been transformed or transfected with expression vectors constructed using recombinant DNA techniques and which contain

sequences encoding the proteins of the present invention. Transformed host cells may express the desired protein (IL-17R or homologs thereof), but host cells transformed for purposes of cloning or amplifying the inventive DNA do not need to express the protein. Expressed proteins will preferably be secreted into the culture supernatant, depending on the DNA selected, but may be deposited in the cell membrane.

Suitable host cells for expression of viral proteins include prokaryotes, yeast or higher eukaryotic cells under the control of appropriate promoters. Prokaryotes include gram negative or gram positive organisms, for example *E. coli* or *Bacillus* spp. Higher eukaryotic cells include established cell lines of mammalian origin as described below. Cell-free translation systems could also be employed to produce viral proteins using RNAs derived from the DNA constructs disclosed herein. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels et al. (*Cloning Vectors: A Laboratory Manual*, Elsevier, New York, 1985), the relevant disclosure of which is hereby incorporated by reference.

Prokaryotic expression hosts may be used for expression of IL-17R or homologs that do not require extensive proteolytic and disulfide processing. Prokaryotic expression vectors generally comprise one or more phenotypic selectable markers, for example a gene encoding proteins conferring antibiotic resistance or supplying an autotrophic requirement, and an origin of replication recognized by the host to ensure amplification within the host. Suitable prokaryotic hosts for transformation include *E. coli*, *Bacillus subtilis*, *Salmonella typhimurium*, and various species within the genera *Pseudomonas*, *Streptomyces*, and *Staphylococcus*, although others may also be employed as a matter of choice.

Recombinant IL-17R may also be expressed in yeast hosts, preferably from the *Saccharomyces* species, such as *S. cerevisiae*. Yeast of other genera, such as *Pichia* or *Kluyveromyces* may also be employed. Yeast vectors will generally contain an origin of replication from the 2 μ yeast plasmid or an autonomously replicating sequence (ARS), promoter, DNA encoding the viral protein, sequences for polyadenylation and transcription termination and a selection gene. Preferably, yeast vectors will include an origin of replication and selectable marker permitting transformation of both yeast and *E. coli*, e.g., the ampicillin resistance gene of *E. coli* and *S. cerevisiae* trp1 gene, which provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, and a promoter derived from a highly expressed yeast gene to induce transcription of a structural sequence downstream. The presence of the trp1 lesion in the yeast host cell genome then provides an effective environment for detecting transformation by growth in the absence of tryptophan.

Suitable yeast transformation protocols are known to those of skill in the art; an exemplary technique is described by Hinnen et al., *Proc. Natl. Acad. Sci. USA* 75:1929,

1978, selecting for Trp⁺ transformants in a selective medium consisting of 0.67% yeast nitrogen base, 0.5% casamino acids, 2% glucose, 10 µg/ml adenine and 20 µg/ml uracil. Host strains transformed by vectors comprising the ADH2 promoter may be grown for expression in a rich medium consisting of 1% yeast extract, 2% peptone, and 1% glucose supplemented with 80 µg/ml adenine and 80 µg/ml uracil. Derepression of the ADH2 promoter occurs upon exhaustion of medium glucose. Crude yeast supernatants are harvested by filtration and held at 4°C prior to further purification.

Various mammalian or insect cell culture systems can be employed to express recombinant protein. Baculovirus systems for production of heterologous proteins in insect cells are reviewed by Luckow and Summers, *Bio/Technology* 6:47 (1988). Examples of suitable mammalian host cell lines include the COS-7 lines of monkey kidney cells, described by Gluzman (*Cell* 23:175, 1981), and other cell lines capable of expressing an appropriate vector including, for example, CV-1/EBNA (ATCC CRL 10478), L cells, C127, 3T3, Chinese hamster ovary (CHO), HeLa and BHK cell lines. Mammalian expression vectors may comprise nontranscribed elements such as an origin of replication, a suitable promoter and enhancer linked to the gene to be expressed, and other 5' or 3' flanking nontranscribed sequences, and 5' or 3' nontranslated sequences, such as necessary ribosome binding sites, a polyadenylation site, splice donor and acceptor sites, and transcriptional termination sequences.

Purification of Receptors for IL-17

Purified IL-17R, homologs, or analogs are prepared by culturing suitable host/vector systems to express the recombinant translation products of the DNAs of the present invention, which are then purified from culture media or cell extracts. For example, supernatants from systems which secrete recombinant protein into culture media can be first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit.

Following the concentration step, the concentrate can be applied to a suitable purification matrix. For example, a suitable affinity matrix can comprise a counter structure protein or lectin or antibody molecule bound to a suitable support. Alternatively, an anion exchange resin can be employed, for example, a matrix or substrate having pendant diethylaminoethyl (DEAE) groups. The matrices can be acrylamide, agarose, dextran, cellulose or other types commonly employed in protein purification. Alternatively, a cation exchange step can be employed. Suitable cation exchangers include various insoluble matrices comprising sulfopropyl or carboxymethyl groups. Sulfopropyl groups are preferred. Gel filtration chromatography also provides a means of purifying the inventive proteins.

Affinity chromatography is a particularly preferred method of purifying IL-17R and homologs thereof. For example, a IL-17R expressed as a fusion protein comprising an immunoglobulin Fc region can be purified using Protein A or Protein G affinity chromatography. Moreover, a IL-17R protein comprising an oligomerizing zipper domain
5 may be purified on a resin comprising an antibody specific to the oligomerizing zipper domain. Monoclonal antibodies against the IL-17R protein may also be useful in affinity chromatography purification, by utilizing methods that are well-known in the art. A ligand (i.e., IL-17 or HVS-13) may also be used to prepare an affinity matrix for affinity purification of IL-17R.

10 Finally, one or more reversed-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify a IL-17R composition. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a homogeneous recombinant protein.

15 Recombinant protein produced in bacterial culture is usually isolated by initial extraction from cell pellets, followed by one or more concentration, salting-out, aqueous ion exchange or size exclusion chromatography steps. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps. Microbial cells employed in expression of recombinant viral protein can be disrupted by any convenient
20 method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.

Fermentation of yeast which express the inventive protein as a secreted protein greatly simplifies purification. Secreted recombinant protein resulting from a large-scale fermentation can be purified by methods analogous to those disclosed by Urdal et al. (*J. Chromatog.* 296:171, 1984). This reference describes two sequential, reversed-phase
25 HPLC steps for purification of recombinant human GM-CSF on a preparative HPLC column.

Protein synthesized in recombinant culture is characterized by the presence of cell components, including proteins, in amounts and of a character which depend upon the
30 purification steps taken to recover the inventive protein from the culture. These components ordinarily will be of yeast, prokaryotic or non-human higher eukaryotic origin and preferably are present in innocuous contaminant quantities, on the order of less than about 1 percent by weight. Further, recombinant cell culture enables the production of the
35 inventive proteins free of other proteins which may be normally associated with the proteins as they are found in nature in the species of origin.

Administration of IL-17R Compositions

The present invention provides methods of using therapeutic compositions comprising an effective amount of a protein and a suitable diluent and carrier, and methods for regulating an immune response. The use of IL-17R or homologs in conjunction with soluble cytokine receptors or cytokines, or other immunoregulatory molecules is also contemplated. Moreover, DNA encoding soluble IL-17R will also be useful; a tissue or organ to be transplanted can be transfected with the DNA by any method known in the art. The organ or tissue thus expresses soluble IL-17R, which acts in the localized area of the graft to suppress rejection of the graft. Similar methods comprising administering such DNA's to the site of the graft will also show efficacy in ameliorating graft rejection.

For therapeutic use, purified protein is administered to a patient, preferably a human, for treatment in a manner appropriate to the indication. Thus, for example, IL-17R protein compositions administered to regulate immune function can be given by bolus injection, continuous infusion, sustained release from implants, or other suitable technique. Typically, a therapeutic agent will be administered in the form of a composition comprising purified IL-17R, in conjunction with physiologically acceptable carriers, excipients or diluents. Such carriers will be nontoxic to recipients at the dosages and concentrations employed.

Ordinarily, the preparation of such protein compositions entails combining the inventive protein with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrans, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are exemplary appropriate diluents. Preferably, product is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Appropriate dosages can be determined in trials. The amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient, and so forth.

Receptors for IL-17 (CTLA-8) can be administered for the purpose of inhibiting T cell proliferation, or for inhibiting T cell activation. Soluble IL-17R are thus likely to be useful in preventing or treating organ or graft rejection, autoimmune disease, allergy or asthma. The inventive receptor proteins will also be useful for prevention or treatment of inflammatory disease in which activated T cells play a role. Similarly, HVS13 and homologs thereof stimulate B cell proliferation and immunoglobulin secretion; thus, receptors that bind HVS13 or CTLA-8 will be useful *in vivo* to inhibit B cell proliferation or immunoglobulin secretion. Receptors for CTLA-8 will also be useful to inhibit the binding of HVS13 or CTLA-8 to cells expressing IL-17R.

The following examples are offered by way of illustration, and not by way of limitation. Those skilled in the art will recognize that variations of the invention embodied in the examples can be made, especially in light of the teachings of the various references cited herein, the disclosures of which are incorporated by reference.

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EXAMPLE 1

This example describes identification of cells that express a receptor (or counterstructure) for HVS13/mCTLA8. A chimeric protein (HVS13 type II Fc) consisting of an Fc region of a human immunoglobulin (SEQ ID NO:4) followed by the amino acid 19 to 151 of HVS 13 (SEQ ID NO:8) was prepared. A murine CTLA8/Fc (mCTLA8/Fc) was constructed by fusing amino acid 22 to 150 of mCTLA8 (SEQ ID NO:6) to the Fc region of human IgG1. A control Fc protein was constructed by a similar method. The HVS13/Fc and mCTLA-8 proteins were expressed and used to identify cell sources by flow cytometry.

15 Cells (1×10^6) were preincubated on ice for 30 minutes in 100 μ l of FACS buffer (PBS, 1% FCS and 0.1% NaN₃) containing 2% normal goat serum and 2% normal rabbit serum to block nonspecific binding. 100 μ l of HVS 13/Fc, mCTLA-8/Fc or control/Fc protein was added at 5 μ g/ml and incubated on ice for 30 min. After washing, the cells were stained with biotin labeled anti human IgG (Fc specific) followed by PE-conjugated streptavidin (Becton Dickson & Co, Mountain View, CA) in 100 μ l of FACS buffer. Cells were then washed and analyzed using a FACScan (Becton Dickinson). A minimum of 5,000 cells were analyzed for each sample. More than a dozen cell lines were screened and it was found that both HVS13/Fc and mCTLA8/Fc fusion proteins bound specifically to the murine thymoma cell line EL4. These cells did not bind to the control/Fc fusion protein.

25

EXAMPLE 2

This example describes cloning of the gene that encodes IL-17R. After identification of a source for HVS13 counterstructure, an EL4 mammalian expression library was screened by a slide-binding autoradiographic method (Gearing et al., *EMBO J.* 8:3667, 1989). CV1/EBNA cells were maintained in Dulbecco's modified Eagle's medium (DMEM) containing 10% (v/v) fetal calf serum (FCS) at 37°C in a humidified atmosphere containing 10% CO₂ and passaged twice weekly. Subconfluent CV1/EBNA cell monolayers on fibronectin-treated chamber slides (Labtek) were transfected by a chloroquine-mediated DEAE-dextran procedure with plasmid DNAs derived from pooled transformants (2,000 transformants per pool) of murine EL4 cDNA library.

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The CV1/EBNA cells transfected with the murine EL4 cDNA pools were assayed for HVS13/Fc binding two days after transfection using [¹²⁵I] labeled goat anti-human IgG

binding and slide autoradiography. Transfected cell monolayers were washed with binding medium (RPMI 1640 containing 1% bovine serum albumin and 50 mg/ml non-fat dry milk), then incubated with 1 µg/ml of HVS13/Fc for one hour at room temperature. Cells were washed, incubated with ¹²⁵I-labeled goat anti-human IgG (New England nuclear, Cambridge, MA). Cells were washed twice with binding medium, three times with PBS, and fixed in PBS containing 2.5% glutaraldehyde for 30 minutes, washed twice more with PBS and air dried. The chamber slides were then dipped in Kodak GTNB-2 photographic emulsion and exposed for 3 days at 4°C before developing.

Forty pools of approximately 2,000 cDNA each were transfected into CV1/EBNA cells. Two pools of cDNA were found to confer binding to HVS13/Fc protein. These pools were broken down to pools of 100 cDNAs, and subsequently to individual clones. Two single cDNA clones were isolated. These clones were transfected into CV1/EBNA to determine whether the protein encoded thereby conferred binding to both HVS13/Fc and mCTLA8/Fc. Both HVS/Fc and mCTLA8/Fc bound to CV1/EBNA cells transfected with the cloned cDNA, but not to cells transfected with empty vector. Control/Fc did not bind to either of them.

Sequencing of these clones found that they contained a 3.2 kb and 1.7 kb insert derived from same mRNA. The 3.2 kb clone contained an open reading frame of 2595 bp surrounded by 120 bp at the 5' noncoding sequence and 573 bp of 3' noncoding sequence. There were no in-frame stop codons upstream of the predicted initiator methionine, which is preceded by a purine residue (guanine) at -3 position, the most important indicator of a good translation initiation site (Kozak, *Mol. Cell. Biol.* 9:5134, 1989). It also has a guanine at +4 position, making it an optimal for translation initiation. The open reading frame is predicted to encode a type I transmembrane protein of 864 amino acids. The nucleotide and predicted amino acid sequence is shown in SEQ ID NOs:1 and 2.

Computer analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 31 and 32. The signal peptide is followed by a 291 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 521 amino acid cytoplasmic tail. There are eight potential N-linked glycosylation sites in the extracellular domain of the protein. The predicted molecular weight for this protein is 97.8 kilodaltons with an estimated isoelectric point of 4.85. Comparison of both nucleotide and amino acid sequences with the GenBank or EMBL databases found no significant homology with known nucleotide and protein sequences.

In order to determine the cellular and tissue distribution of IL-17R mRNA, poly(A)⁺ RNA derived from various murine cell lines or tissues was examined by Northern blot analysis using the IL-17R cDNA as a probe. Filters containing poly(A)⁺ RNA (2 µg per lane) from various tissues were purchased from Clontech (Palo Alto, CA).

Polyadenylated RNA from various cells or cell lines were isolated, fractionated (2 µg per lane) on a 1% agarose formaldehyde gel, blotted onto Hybond nylon membrane (Amersham). Filters were probed with an anti-sense RNA riboprobe corresponding to the coding region of IL-17R cDNA. Hybridization was performed at 63°C followed by three washings in 0.2% x SSC, 0.1% SDS at 68°C. Blots were exposed for 8 to 48 hr at -70°C.

The IL-17R probe hybridized to a single species of mRNA of approximately 3.7 kb in all tissues. Among the tissues examined, strong hybridizing signals were observed in spleen and kidney. Moderate signals were observed in lung and liver, and weaker signals in brain, heart, skeletal muscle and testes. Similar size mRNAs were detected in the following cells and cell lines: fetal liver epithelial cells (D11), fibroblast (3T3), rat intestinal epithelial cells (1CE6), splenic B cells, muscle cells (BB4), mast cells (H7), triple negative thymus cells (TN), pre-B cells (70Z/3), T cell hybridoma (EL4); and T cell clones 7C2 and D10. All the cell lines tested were found to express IL-17R mRNA, suggesting a ubiquitous expression of IL-17R message.

EXAMPLE 3

This example describes construction of a construct to express a soluble IL-17R/Flag® protein referred to as IL-17R/Flag. IL-17R/Flag® contains a leader sequence, and the region of IL-17R from amino acid 1 to amino acid 322 (SEQ ID NO:1), and the octapeptide referred to as Flag® (SEQ ID NO:3). The construct is prepared essentially as described for other soluble constructs, by ligating a DNA fragment encoding amino acids 1 through 322 of SEQ ID NO:1 (prepared as described in Example 4) into an appropriate expression vector which contains a suitable leader sequence. The resultant DNA construct is transfected into a suitable cell line such as the monkey kidney cell line CV-1/EBNA (ATCC CRL 10478). IL-17R/Flag® may be purified using a Flag® antibody affinity column, and analyzed for biological activity using any of the methods described herein.

EXAMPLE 4

This example describes construction of a IL-17R DNA construct to express a IL-17R/Fc fusion protein. A soluble form of IL-17R fused to the Fc region of human IgG1 was constructed in the mammalian expression vector pDC409 in the following way: A pair of oligonucleotide primers containing a sense sequence and an antisense sequence of IL-17R were synthesized. The sense primer contained a Sal I site at the 5' end of the cDNA and antisense primer contained a Bgl II site and contained the IL-17R truncated just before the transmembrane region and a stop codon. A 980 bp DNA fragment was amplified from IL-17R cDNA. The PCR product was cut with Sal I and Bgl II and used in a three way

ligation with a fragment carrying the human IgG1 region cut with Bgl II and Not I into a plasmid (pDC409; see USSN 08/235,397) previously cut with Sal I and Not I. The encoded insert contained the nucleotides encoding the amino acid sequence of residues 1 to 322 of IL-17R (SEQ ID NO:1). The sequence was confirmed by sequencing the whole region.

The IL-17R/Fc expression plasmids were transfected into CV-1/EBNA cells, and supernatants were collected for 1 week. The CTLA-8/Fc fusion proteins were purified on a protein A sepharose column (Pharmacia, Uppsala, Sweden) as described below. Protein concentration was determined by an enzyme-linked immunoadsorbent assay specific for the constant domain of human IgG1 and by BCA analysis (Pharmacia), and purity was confirmed by SDS-polyacrylamide gel electrophoresis analysis followed by silver stain of the gel.

EXAMPLE 5

This example describes purification of IL-17R fusion proteins. IL-17R/Fc fusion protein is purified by conventional methods using Protein A or Protein G chromatography. Approximately one liter of culture supernatant containing IL-17R/Fc fusion protein is purified by filtering mammalian cell supernatants (e.g., in a 0.45m filter) and applying filtrate to a protein A/G antibody affinity column (Schleicher and Schuell, Keene, NH) at 4°C at a flow rate of 80 ml/hr for a 1.5 cm x 12.0 cm column. The column is washed with 0.5 M NaCl in PBS until free protein is not detected in the wash buffer. Finally, the column is washed with PBS. Bound fusion protein is eluted from the column with 25 mM citrate buffer, pH 2.8, and brought to pH 7 with 500 mM Hepes buffer, pH 9.1.

A IL-17R fusion protein comprising Flag® may also be detected and/or purified using an antibody that binds Flag®, substantially as described in Hopp et al., *Bio/Technology* 6:1204 (1988). Biological activity is measured by inhibition of CTLA-8 activity in any biological assay which quantifies the co-stimulatory effect of CTLA-8, for example, as described in the Examples herein.

EXAMPLE 6

This example illustrates the preparation of monoclonal antibodies against IL-17R. Preparations of purified recombinant IL-17R, for example, or transfected cells expressing high levels of IL-17R, are employed to generate monoclonal antibodies against IL-17R using conventional techniques, such as those disclosed in U.S. Patent 4,411,993. Such antibodies are likely to be useful in interfering with IL-17R binding to CTLA-8, as components of diagnostic or research assays for IL-17R, or in affinity purification of IL-17R.

To immunize rodents, IL-17R immunogen is emulsified in an adjuvant (such as complete or incomplete Freund's adjuvant, alum, or another adjuvant, such as Ribi adjuvant R700 (Ribi, Hamilton, MT), and injected in amounts ranging from 10-100 μ g subcutaneously into a selected rodent, for example, BALB/c mice or Lewis rats. Ten days to three weeks days later, the immunized animals are boosted with additional immunogen and periodically boosted thereafter on a weekly, biweekly or every third week immunization schedule. Serum samples are periodically taken by retro-orbital bleeding or tail-tip excision for testing by dot-blot assay (antibody sandwich), ELISA (enzyme-linked immunosorbent assay), immunoprecipitation, or other suitable assays, including FACS analysis. Following detection of an appropriate antibody titer, positive animals are given an intravenous injection of antigen in saline. Three to four days later, the animals are sacrificed, splenocytes harvested, and fused to a murine myeloma cell line (e.g., NS1 or preferably Ag 8.653 [ATCC CRL 1580]). Hybridoma cell lines generated by this procedure are plated in multiple microtiter plates in a selective medium (for example, one containing hypoxanthine, aminopterin, and thymidine, or HAT) to inhibit proliferation of non-fused cells, myeloma-myeloma hybrids, and splenocyte-splenocyte hybrids.

Hybridoma clones thus generated can be screened by ELISA for reactivity with IL-17R, for example, by adaptations of the techniques disclosed by Engvall et al., *Immunochem.* 8:871 (1971) and in U.S. Patent 4,703,004. A preferred screening technique is the antibody capture technique described by Beckman et al., *J. Immunol.* 144:4212 (1990). Positive clones are then injected into the peritoneal cavities of syngeneic rodents to produce ascites containing high concentrations (>1 mg/ml) of anti-IL-17R monoclonal antibody. The resulting monoclonal antibody can be purified by ammonium sulfate precipitation followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can also be used, as can affinity chromatography based upon binding to IL-17R protein.

EXAMPLE 7

This example illustrates the ability of IL-17R to inhibit the proliferative response of T cells to mitogens. Lymphoid organs were harvested aseptically and cell suspension was created. Splenic and lymph node T cells were isolated from the cell suspension. The purity of the resulting splenic T cell preparations was routinely >95% CD3⁺ and <1% sIgM⁺. Purified murine splenic T cells (2x10⁵/well) were cultured with either 1% PHA or 1 μ g/ml Con A, and a soluble IL-17R was titrated into the assay. Proliferation was determined after 3 days with the addition of 1 μ Ci [³H]thymidine. Secretion of cytokines (Interleukin-2) was determined for murine T cells cultured for 24 hr with 1 μ g/ml of Con A in the presence or absence of 10 μ g/ml of IL-17R.Fc or in the presence of a control Fc

protein. IL-2 production was measured by ELISA and results expressed as ng/ml IL-2 produced.

Soluble IL-17R/Fc significantly inhibited the mitogen-induced proliferation of purified murine splenic T cells in a dose dependent manner, while a control Fc had no effect on the murine T cell proliferation. Complete inhibition of mitogen induced proliferation was observed at a soluble IL-17R.Fc concentration of 10 µg/ml. Analysis of IL-2 production by splenic T cells activated with Con A in the presence or absence of IL-17R.Fc in the culture revealed that addition of IL-17R.Fc to the T-cell culture inhibited IL-2 production to levels 8-9-fold lower than those observed in cultures containing media alone or media plus a control Fc protein. Similar results were observed when purified human T cells were used.

EXAMPLE 8

This example presents the isolation of a DNA encoding human IL-17R by cross species hybridization. A human peripheral blood lymphocyte library was prepared and screened substantially as described in USSN 08/249,189, using murine IL-17R DNA under moderately high stringency conditions. Several clones of varying length were obtained. Sequencing data indicated that the human IL-17R was approximately 76% identical to murine IL-17R at the nucleotide level. The nucleotide and predicted amino acid sequence of human IL-17R is shown in SEQ ID NOs:10 and 11. A plasmid (pGEMBL) containing DNA encoding the human IL-17 receptor (referred to as pGEMBL-HuIL-17R) in *E. coli* DH10, was deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852-1776, USA, on June 5, 1995, under the conditions of the Budapest Treaty, and assigned accession number 69834.

The human IL-17R shared many features with the murine IL-17 R. Computer analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 27 and 28. The signal peptide is followed by a 293 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 525 amino acid cytoplasmic tail. Soluble IL-17R comprises the signal peptide and the extracellular domain (residues 1 to 320 of SEQ ID NO:1) or a fragment thereof. Alternatively, a different signal peptide can be substituted for the native signal peptide. A Type I Fc fusion protein (wherein DNA encoding the Fc region of an immunoglobulin molecule is fused to DNA encoding the IL-17R immediately before, and in place of, the DNA encoding the transmembrane region of the IL-17R) was prepared, substantially as described in Example 4. A soluble hIL-17R protein can be also expressed substantially as described in Example 3, or by any other method of preparing and expressing the extracellular domain of IL-17R or a fragment thereof..

EXAMPLE 9

This example presents the localization and fine mapping of the murine IL-17R gene. A panel of DNA samples from an interspecific cross that has been characterized for over 900 genetic markers throughout the genome was analyzed. The genetic markers
5 included in this map span between 50 and 80 centi-Morgans on each mouse autosome and the X chromosome (Chr) (Saunders and Seldin, *Genomics* 8:524, 1990; Watson et al., *Mammalian Genome* 2:158, 1992).

Initially, DNA from the two parental mice [C3H/HeJ-*gld* and (C3H/HeJ-*gld* x *Mus spretus*) F1] were digested with various restriction endonucleases and hybridized with the
10 IL-17R cDNA probe to determine restriction fragment length variants (RFLVs) to allow haplotype analyses. Informative *Bgl*I RFLVs were detected: C3H/HeJ-*gld*, 10.0 kb; *Mus spretus*, 7.8 kb and 2.2 kb). In each of the backcross mice either the C3H/HeJ-*gld* parental band or all three bands (both *Mus spretus* bands and a half intensity C3H/HEJ-*gld* band) were observed indicating that a single locus was detected.

15 Comparison of the haplotype distribution of the IL-17R RFLVs indicated that this gene cosegregated in 111 of the 114 meiotic events examined with the *Raf*I gene locus on mouse Chr 6. The best gene order (Bishop, *Genet. Epidemiol.* 2:349, 1985) \pm the standard deviation (Green, In Genetics and Probability in Animal Breeding Experiments. E. Green, ed.; Macmillan, New York, pp.77-113, 1981) was: (centromere) *Raf*I-2.6 cM \pm
20 1.5 cM - *IL-17R* - 2.5 cM \pm 1.5 cM - *Cd4*.

EXAMPLE 10

This example demonstrates that soluble IL-17R suppresses rejection of organ grafts *in vivo*. Hearts from neonatal C57BL/6 (H-2^b) mice (less than 24 hours old) were
25 transplanted into the ear pinnae of adult BALB/c (H-2^d) recipients substantially as described in U.S. patent 5,492,888, issued February 20, 1996 (utilizing the method of Fulmer et al., *Am. J. Anat.* 113:273, 1963, modified as described by Trager et al., *Transplantation* 47:587, 1989, and Van Buren et al., *Transplant. Proc.* 15:2967, 1983). Survival of the transplanted hearts was assessed by visually inspecting the grafts for pulsatile activity, as
30 determined by examining the ear-heart grafts of anesthetized recipients under a dissecting microscope with soft reflected light beginning on day 5 or 6 post transplant. The time of graft rejection was defined as the day after transplantation on which contractile activity ceased.

In one set of experiments, neonatal hearts were removed, rinsed with sterile PBS to
35 remove excess blood, and placed into prepared ear pinnae. Recipient mice were given either soluble murine IL-17R/Fc (100 μ g in 200 μ l; see Example 4 herein) or rat IgG as a control, i.p. on days 0 through 3 post transplantation. In a second set of experiments, the

recipient mice were injected with IL-17R or human IgG on days 0, 1 and 2; the quantity and route of injection were as done previously. The results of these experiments are shown in Table 1.

5

Table 1: Effects of Soluble Murine IL-17R (smuIL-17R) on Neovascularized Heterotopic Cardiac Allograft Survival

	Treatment Group	Survival Time (days)	Median Survival Time \pm S. D.
Experiment 1	rat IgG	11, 14, 14, 14	13 \pm 1.5
	smuIL-17R	19, 19, 19, 21	20 \pm 1.0
Experiment 2	human IgG	13, 13, 13, 15	14 \pm 1.0
	smuIL-17R	20, 20, 20, 20	20 \pm 0.0

Table 1 shows that heart allografts survived approximately 13 days in individual control mice treated with rat IgG. When allograft recipients were given up to four daily injections of soluble IL-17R, graft survival was prolonged, with a median survival of 20, approximately seven days longer than the survival time of identical grafts in control mice. When a prolonged release of the IL-17R was obtained by encapsulating the soluble IL-17R in alginate beads, it was observed that a single administration of 100 μ g soluble IL-17R prolonged graft survival in much the same manner as observed previously with soluble IL-17R in solution. These results demonstrate that soluble IL-17R suppresses rejection of grafted tissues.

EXAMPLE 11

This example demonstrates that DNA encoding soluble IL-17R will be useful in suppressing rejection of organ grafts *in vivo*. Hearts from neonatal C57BL/6 (H-2^b) mice were transplanted into the ear pinnae of adult BALB/c (H-2^d) recipients as described in Example 10 above, except that the hearts were injected with 15 μ l of PBS containing either IL-17R/Fc-encoding DNA (pDC409-IL-17R; Example 4) or control DNA (empty pDC409) at a concentration of about 1 mg/ml, into a ventricle. A 30 gauge needle was used, and care was taken to minimize trauma to the heart. The transfected hearts were then transplanted into BALB/c recipients and graft survival determined as described previously. Results are presented in Table 2.

Table 2: Effects of Expression of Soluble Murine IL-17R by Cardiac Cells on Neovascularized Heterotopic Cardiac Allograft Survival

Treatment Group	Survival Time (days)	Median Survival Time \pm S. D.
rat IgG	13, 15, 15, 15, 18	15 ± 1.8
smuIL-17R	20, 25, 28, >60, >60	ND*

*ND: Not done; median survival time could not be calculated since two mice still show pulsatile grafts more than two months after transplantation.

5

Table 2 shows that heart allografts survived approximately 15 days in individual control mice transplanted with hearts transfected with empty vector. When the transplanted hearts were transfected with DNA encoding soluble IL-17R, graft survival was prolonged. For three of the five mice in this group, grafts survived on average approximately 24 days, nine days longer than the survival time of identical grafts in control mice. The grafts given the other two mice were still pulsatile (i.e., had not been rejected) more than 60 days post transplant., and had apparently been accepted by the recipients. These results demonstrate that transfecting tissues to be grafted with DNA encoding soluble IL-17R ameliorates rejection of those tissues by the recipient.

15

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- 5 (i) APPLICANT: Yao, Zhengbin
Spriggs, Melanie
Fanslow, William
- 10 (ii) TITLE OF INVENTION: Novel Receptor That Binds IL-17
- (iii) NUMBER OF SEQUENCES: 10
- 15 (iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Immunex Corporation
(B) STREET: 51 University Street
(C) CITY: Seattle
(D) STATE: WA
(E) COUNTRY: USA
20 (F) ZIP: 98101
- (v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: Apple Macintosh
25 (C) OPERATING SYSTEM: Apple Operating System 7.1
(D) SOFTWARE: Microsoft Word for Apple, Version 5.1a
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- (viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Perkins, Patricia Anne
45 (B) REGISTRATION NUMBER: 34,695
(C) REFERENCE/DOCKET NUMBER: 2617-WO
- (ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (206)587-0430
50 (B) TELEFAX: (206)

(2) INFORMATION FOR SEQ ID NO:1:

- 55 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3288 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

5 (iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

10 (A) ORGANISM: Mouse

(B) CLONE: HVS13 receptor

(ix) FEATURE:

15 (A) NAME/KEY: CDS

(B) LOCATION: 121..2715

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

20	GTCGACTGGA ACGAGACGAC CTGCTGCCGA CGAGCGCCAG TCCTCGGCCG GGAAAGCCAT	60
	CGCGGGCCCT CGCTGTCGCG CGGAGCCAGC TGCAGCGCT CCGCGACCGG GCCGAGGGCT	120
25	ATG GCG ATT CGG CGC TGC TGG CCA CGG GTC GTC CCC GGG CCC GCG CTG	168
	Met Ala Ile Arg Arg Cys Trp Pro Arg Val Val Pro Gly Pro Ala Leu	
	1 5 10 15	
30	GGA TGG CTG CTT CTG CTG CTG AAC GTT CTG GCC CCG GGC CGC GCC TCC	216
	Gly Trp Leu Leu Leu Leu Asn Val Leu Ala Pro Gly Arg Ala Ser	
	20 25 30	
	CCG CGC CTC CTC GAC TTC CCG GCT CCG GTC TGC GCG CAG GAG GGG CTG	264
	Pro Arg Leu Leu Asp Phe Pro Ala Pro Val Cys Ala Gln Glu Gly Leu	
	35 40 45	
35	AGC TGC AGA GTC AAG AAT AGT ACT TGT CTG GAT GAC AGC TGG ATC CAC	312
	Ser Cys Arg Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His	
	50 55 60	
40	CCC AAA AAC CTG ACC CCG TCT TCC CCA AAA AAC ATC TAT ATC AAT CTT	360
	Pro Lys Asn Leu Thr Pro Ser Ser Pro Lys Asn Ile Tyr Ile Asn Leu	
	65 70 75 80	
45	AGT GTT TCC TCT ACC CAG CAC GGA GAA TTA GTC CCT GTG TTG CAT GTT	408
	Ser Val Ser Ser Thr Gln His Gly Glu Leu Val Pro Val Leu His Val	
	85 90 95	
50	GAG TGG ACC CTG CAG ACA GAT GCC AGC ATC CTG TAC CTC GAG GGT GCA	456
	Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala	
	100 105 110	
	GAG CTG TCC GTC CTG CAG CTG AAC ACC AAT GAG CGG CTG TGT GTC AAG	504
	Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Lys	
	115 120 125	
55	TTC CAG TTT CTG TCC ATG CTG CAG CAT CAC CGT AAG CGG TGG CGG TTT	552
	Phe Gln Phe Leu Ser Met Leu Gln His His Arg Lys Arg Trp Arg Phe	
	130 135 140	

	TCC	TTC	AGC	CAC	TTT	GTG	GTA	GAT	CCT	GGC	CAG	GAG	TAT	GAA	GTG	ACT	600
	Ser	Phe	Ser	His	Phe	Val	Val	Asp	Pro	Gly	Gln	Glu	Tyr	Glu	Val	Thr	
	145					150					155					160	
5	GTT	CAC	CAC	CTG	CCG	AAG	CCC	ATC	CCT	GAT	GGG	GAC	CCA	AAC	CAC	AAA	648
	Val	His	His	Leu	Pro	Lys	Pro	Ile	Pro	Asp	Gly	Asp	Pro	Asn	His	Lys	
					165					170					175		
10	TCC	AAG	ATC	ATC	TTT	GTG	CCT	GAC	TGT	GAG	GAC	AGC	AAG	ATG	AAG	ATG	696
	Ser	Lys	Ile	Ile	Phe	Val	Pro	Asp	Cys	Glu	Asp	Ser	Lys	Met	Lys	Met	
				180					185					190			
15	ACT	ACC	TCA	TGC	GTG	AGC	TCA	GGC	AGC	CTT	TGG	GAT	CCC	AAC	ATC	ACT	744
	Thr	Thr	Ser	Cys	Val	Ser	Ser	Gly	Ser	Leu	Trp	Asp	Pro	Asn	Ile	Thr	
			195					200					205				
20	GTG	GAG	ACC	TTG	GAC	ACA	CAG	CAT	CTG	CGA	GTG	GAC	TTC	ACC	CTG	TGG	792
	Val	Glu	Thr	Leu	Asp	Thr	Gln	His	Leu	Arg	Val	Asp	Phe	Thr	Leu	Trp	
		210					215					220					
	AAT	GAA	TCC	ACC	CCC	TAC	CAG	GTC	CTG	CTG	GAA	AGT	TTC	TCC	GAC	TCA	840
	Asn	Glu	Ser	Thr	Pro	Tyr	Gln	Val	Leu	Leu	Glu	Ser	Phe	Ser	Asp	Ser	
	225					230					235					240	
25	GAG	AAC	CAC	AGC	TGC	TTT	GAT	GTC	GTT	AAA	CAA	ATA	TTT	GCG	CCC	AGG	888
	Glu	Asn	His	Ser	Cys	Phe	Asp	Val	Val	Lys	Gln	Ile	Phe	Ala	Pro	Arg	
					245					250					255		
30	CAA	GAA	GAA	TTC	CAT	CAG	CGA	GCT	AAT	GTC	ACA	TTC	ACT	CTA	AGC	AAG	936
	Gln	Glu	Glu	Phe	His	Gln	Arg	Ala	Asn	Val	Thr	Phe	Thr	Leu	Ser	Lys	
				260					265					270			
35	TTT	CAC	TGG	TGC	TGC	CAT	CAC	CAC	GTG	CAG	GTC	CAG	CCC	TTC	TTC	AGC	984
	Phe	His	Trp	Cys	Cys	His	His	His	Val	Gln	Val	Gln	Pro	Phe	Phe	Ser	
			275					280					285				
40	AGC	TGC	CTA	AAT	GAC	TGT	TTG	AGA	CAC	GCT	GTG	ACT	GTG	CCC	TGC	CCA	1032
	Ser	Cys	Leu	Asn	Asp	Cys	Leu	Arg	His	Ala	Val	Thr	Val	Pro	Cys	Pro	
		290					295					300					
	GTA	ATC	TCA	AAT	ACC	ACA	GTT	CCC	AAG	CCA	GTT	GCA	GAC	TAC	ATT	CCC	1080
	Val	Ile	Ser	Asn	Thr	Thr	Val	Pro	Lys	Pro	Val	Ala	Asp	Tyr	Ile	Pro	
	305					310					315					320	
45	CTG	TGG	GTG	TAT	GGC	CTC	ATC	ACA	CTC	ATC	GCC	ATT	CTG	CTG	GTG	GGA	1128
	Leu	Trp	Val	Tyr	Gly	Leu	Ile	Thr	Leu	Ile	Ala	Ile	Leu	Leu	Val	Gly	
					325					330					335		
50	TCT	GTC	ATC	GTG	CTG	ATC	ATC	TGT	ATG	ACC	TGG	AGG	CTT	TCT	GGC	GCC	1176
	Ser	Val	Ile	Val	Leu	Ile	Ile	Cys	Met	Thr	Trp	Arg	Leu	Ser	Gly	Ala	
				340					345					350			
55	GAT	CAA	GAG	AAA	CAT	GGT	GAT	GAC	TCC	AAA	ATC	AAT	GGC	ATC	TTG	CCC	1224
	Asp	Gln	Glu	Lys	His	Gly	Asp	Asp	Ser	Lys	Ile	Asn	Gly	Ile	Leu	Pro	
			355					360					365				
60	GTA	GCA	GAC	CTG	ACT	CCC	CCA	CCC	CTG	AGG	CCC	AGG	AAG	GTC	TGG	ATC	1272
	Val	Ala	Asp	Leu	Thr	Pro	Pro	Pro	Leu	Arg	Pro	Arg	Lys	Val	Trp	Ile	
		370					375					380					

	GTC TAC TCG GCC GAC CAC CCC CTC TAT GTG GAG GTG GTC CTA AAG TTC	1320
	Val Tyr Ser Ala Asp His Pro Leu Tyr Val Glu Val Val Leu Lys Phe	
	385 390 395 400	
5	GCC CAG TTC CTG ATC ACT GCC TGT GGC ACT GAA GTA GCC CTT GAC CTC	1368
	Ala Gln Phe Leu Ile Thr Ala Cys Gly Thr Glu Val Ala Leu Asp Leu	
	405 410 415	
10	CTG GAA GAG CAG GTT ATC TCT GAG GTG GGG GTC ATG ACC TGG GTG AGC	1416
	Leu Glu Glu Gln Val Ile Ser Glu Val Gly Val Met Thr Trp Val Ser	
	420 425 430	
15	CGA CAG AAG CAG GAG ATG GTG GAG AGC AAC TCC AAA ATC ATC ATC CTG	1464
	Arg Gln Lys Gln Glu Met Val Glu Ser Asn Ser Lys Ile Ile Leu	
	435 440 445	
20	TGT TCC CGA GGC ACC CAA GCA AAG TGG AAA GCT ATC TTG GGT TGG GCT	1512
	Cys Ser Arg Gly Thr Gln Ala Lys Trp Lys Ala Ile Leu Gly Trp Ala	
	450 455 460	
25	GAG CCT GCT GTC CAG CTA CGG TGT GAC CAC TGG AAG CCT GCT GGG GAC	1560
	Glu Pro Ala Val Gln Leu Arg Cys Asp His Trp Lys Pro Ala Gly Asp	
	465 470 475 480	
30	CTT TTC ACT GCA GCC ATG AAC ATG ATC CTG CCA GAC TTC AAG AGG CCA	1608
	Leu Phe Thr Ala Ala Met Asn Met Ile Leu Pro Asp Phe Lys Arg Pro	
	485 490 495	
35	GCC TGC TTC GGC ACC TAC GTT GTT TGC TAC TTC AGT GGC ATC TGT AGT	1656
	Ala Cys Phe Gly Thr Tyr Val Val Cys Tyr Phe Ser Gly Ile Cys Ser	
	500 505 510	
40	GAG AGG GAT GTC CCC GAC CTC TTC AAC ATC ACC TCC AGG TAC CCA CTC	1704
	Glu Arg Asp Val Pro Asp Leu Phe Asn Ile Thr Ser Arg Tyr Pro Leu	
	515 520 525	
45	ATG GAC AGA TTT GAG GAG GTT TAC TTC CGG ATC CAG GAC CTG GAG ATG	1752
	Met Asp Arg Phe Glu Glu Val Tyr Phe Arg Ile Gln Asp Leu Glu Met	
	530 535 540	
50	TTT GAA CCC GGC CGG ATG CAC CAT GTC AGA GAG CTC ACA GGG GAC AAT	1800
	Phe Glu Pro Gly Arg Met His His Val Arg Glu Leu Thr Gly Asp Asn	
	545 550 555 560	
55	TAC CTG CAG AGC CCT AGT GGC CGG CAG CTC AAG GAG GCT GTG CTT AGG	1848
	Tyr Leu Gln Ser Pro Ser Gly Arg Gln Leu Lys Glu Ala Val Leu Arg	
	565 570 575	
60	TTC CAG GAG TGG CAA ACC CAG TGC CCC GAC TGG TTC GAG CGT GAG AAC	1896
	Phe Gln Glu Trp Gln Thr Gln Cys Pro Asp Trp Phe Glu Arg Glu Asn	
	580 585 590	
65	CTC TGC TTA GCT GAT GGC CAA GAT CTT CCC TCC CTG GAT GAA GAA GTG	1944
	Leu Cys Leu Ala Asp Gly Gln Asp Leu Pro Ser Leu Asp Glu Glu Val	
	595 600 605	
70	TTT GAA GAC CCA CTG CTG CCA CCA GGG GGA GGA ATT GTC AAA CAG CAG	1992
	Phe Glu Asp Pro Leu Leu Pro Pro Gly Gly Gly Ile Val Lys Gln Gln	
	610 615 620	

	CCC	CTG	GTG	CGG	GAA	CTC	CCA	TCT	GAC	GGC	TGC	CTT	GTG	GTA	GAT	GTC	2040
	Pro	Leu	Val	Arg	Glu	Leu	Pro	Ser	Asp	Gly	Cys	Leu	Val	Val	Asp	Val	
	625					630					635					640	
5	TGT	GTC	AGT	GAG	GAA	GAA	AGT	AGA	ATG	GCA	AAG	CTG	GAC	CCT	CAG	CTA	2088
	Cys	Val	Ser	Glu	Glu	Glu	Ser	Arg	Met	Ala	Lys	Leu	Asp	Pro	Gln	Leu	
					645					650					655		
10	TGG	CCA	CAG	AGA	GAG	CTA	GTG	GCT	CAC	ACC	CTC	CAA	AGC	ATG	GTG	CTG	2136
	Trp	Pro	Gln	Arg	Glu	Leu	Val	Ala	His	Thr	Leu	Gln	Ser	Met	Val	Leu	
				660					665					670			
15	CCA	GCA	GAG	CAG	GTC	CCT	GCA	GCT	CAT	GTG	GTG	GAG	CCT	CTC	CAT	CTC	2184
	Pro	Ala	Glu	Gln	Val	Pro	Ala	Ala	His	Val	Val	Glu	Pro	Leu	His	Leu	
			675					680					685				
20	CCA	GAC	GGC	AGT	GGA	GCA	GCT	GCC	CAG	CTG	CCC	ATG	ACA	GAG	GAC	AGC	2232
	Pro	Asp	Gly	Ser	Gly	Ala	Ala	Ala	Gln	Leu	Pro	Met	Thr	Glu	Asp	Ser	
		690					695					700					
25	GAG	GCT	TGC	CCG	CTG	CTG	GGG	GTC	CAG	AGG	AAC	AGC	ATC	CTT	TGC	CTC	2280
	Glu	Ala	Cys	Pro	Leu	Leu	Gly	Val	Gln	Arg	Asn	Ser	Ile	Leu	Cys	Leu	
	705					710					715					720	
30	CCC	GTG	GAC	TCA	GAT	GAC	TTG	CCA	CTC	TGT	AGC	ACC	CCA	ATG	ATG	TCA	2328
	Pro	Val	Asp	Ser	Asp	Asp	Leu	Pro	Leu	Cys	Ser	Thr	Pro	Met	Met	Ser	
					725					730					735		
35	CCT	GAC	CAC	CTC	CAA	GGC	GAT	GCA	AGA	GAG	CAG	CTA	GAA	AGC	CTA	ATG	2376
	Pro	Asp	His	Leu	Gln	Gly	Asp	Ala	Arg	Glu	Gln	Leu	Glu	Ser	Leu	Met	
				740					745					750			
40	CTC	TCG	GTG	CTG	CAG	CAG	AGC	CTG	AGT	GGA	CAG	CCC	CTG	GAG	AGC	TGG	2424
	Leu	Ser	Val	Leu	Gln	Gln	Ser	Leu	Ser	Gly	Gln	Pro	Leu	Glu	Ser	Trp	
			755					760					765				
45	CCG	AGG	CCA	GAG	GTG	GTC	CTC	GAG	GGC	TGC	ACA	CCC	TCT	GAG	GAG	GAG	2472
	Pro	Arg	Pro	Glu	Val	Val	Leu	Glu	Gly	Cys	Thr	Pro	Ser	Glu	Glu	Glu	
		770					775						780				
50	CAG	CGG	CAG	TCG	GTG	CAG	TCG	GAC	CAG	GGC	TAC	ATC	TCC	AGG	AGC	TCC	2520
	Gln	Arg	Gln	Ser	Val	Gln	Ser	Asp	Gln	Gly	Tyr	Ile	Ser	Arg	Ser	Ser	
						790					795					800	
55	CCG	CAG	CCC	CCC	GAG	TGG	CTC	ACG	GAG	GAG	GAA	GAG	CTA	GAA	CTG	GGT	2568
	Pro	Gln	Pro	Pro	Glu	Trp	Leu	Thr	Glu	Glu	Glu	Glu	Leu	Glu	Leu	Gly	
					805					810					815		
60	GAG	CCC	GTT	GAG	TCT	CTC	TCT	CCT	GAG	GAA	CTA	CGG	AGC	CTG	AGG	AAG	2616
	Glu	Pro	Val	Glu	Ser	Leu	Ser	Pro	Glu	Glu	Leu	Arg	Ser	Leu	Arg	Lys	
				820					825					830			
65	CTC	CAG	AGG	CAG	CTT	TTC	TTC	TGG	GAG	CTC	GAG	AAG	AAC	CCT	GGC	TGG	2664
	Leu	Gln	Arg	Gln	Leu	Phe	Phe	Trp	Glu	Leu	Glu	Lys	Asn	Pro	Gly	Trp	
			835					840					845				
70	AAC	AGC	TTG	GAG	CCA	CGG	AGA	CCC	ACC	CCA	GAA	GAG	CAG	AAT	CCC	TCC	2712
	Asn	Ser	Leu	Glu	Pro	Arg	Arg	Pro	Thr	Pro	Glu	Glu	Gln	Asn	Pro	Ser	
		850					855						860				

TAG GCCTCCTGAG CCTGCTACTT AAGAGGGTGT ATATTGTACT CTGTGTGTGC 2765
 *
 865

5 GTGCGTGTGT GTGTGTGTGT GTGTGTGTGT GTGCGTGTGT GTGTGTGTGT GTGTGTGTGT 2825
 GTGTGTGTAG TGCCCGGCTT AGAAATGTGA ACATCTGAAT CTGACATAGT GTTGTATACC 2885
 10 TGAAGTCCCA GCACTTGGGA ACTGAGACTT GATGATCTCC TGAAGCCAGG TGTTCCAGGGC 2945
 CAGTGTGAAA ACATAGCAAG ACCTCAGAGA AATCAATGCA GACATCTTGG TACTGATCCC 3005
 TAAACACACC CCTTCCCTG ATAACCCGAC ATGAGCATCT GGTCATCATT GCACAAGAAT 3065
 15 CCACAGCCCG TTCCAGAGC TCATAGCCAA GTGTGTTGCT CATTCTTGA ATATTTATTC 3125
 TGTACCTACT ATTCATCAGA CATTGGAAT TCAAAAACAA GTTACATGAC ACAGCCTTAG 3185
 20 CCACTAAGAA GCTTAAAATT CGGTAAGGAT GTAAAATTAG CCAGGATGAA TAGAGGGCTG 3245
 CTGCCCTGGC TGCAGAAGAG CAGGTCGTCT CGTTCAGTC GAC 3288

(2) INFORMATION FOR SEQ ID NO:2:

25

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 865 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

30

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

35 Met Ala Ile Arg Arg Cys Trp Pro Arg Val Val Pro Gly Pro Ala Leu
 1 5 10 15
 Gly Trp Leu Leu Leu Leu Asn Val Leu Ala Pro Gly Arg Ala Ser
 20 25 30
 40 Pro Arg Leu Leu Asp Phe Pro Ala Pro Val Cys Ala Gln Glu Gly Leu
 35 40 45
 45 Ser Cys Arg Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
 50 55 60
 Pro Lys Asn Leu Thr Pro Ser Ser Pro Lys Asn Ile Tyr Ile Asn Leu
 65 70 75 80
 50 Ser Val Ser Ser Thr Gln His Gly Glu Leu Val Pro Val Leu His Val
 85 90 95
 Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
 100 105 110
 55 Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Lys
 115 120 125
 60 Phe Gln Phe Leu Ser Met Leu Gln His His Arg Lys Arg Trp Arg Phe
 130 135 140

	Ser	Phe	Ser	His	Phe	Val	Val	Asp	Pro	Gly	Gln	Glu	Tyr	Glu	Val	Thr	
	145					150					155					160	
5	Val	His	His	Leu	Pro	Lys	Pro	Ile	Pro	Asp	Gly	Asp	Pro	Asn	His	Lys	
					165					170					175		
	Ser	Lys	Ile	Ile	Phe	Val	Pro	Asp	Cys	Glu	Asp	Ser	Lys	Met	Lys	Met	
				180					185					190			
10	Thr	Thr	Ser	Cys	Val	Ser	Ser	Gly	Ser	Leu	Trp	Asp	Pro	Asn	Ile	Thr	
			195					200					205				
	Val	Glu	Thr	Leu	Asp	Thr	Gln	His	Leu	Arg	Val	Asp	Phe	Thr	Leu	Trp	
15		210					215					220					
	Asn	Glu	Ser	Thr	Pro	Tyr	Gln	Val	Leu	Leu	Glu	Ser	Phe	Ser	Asp	Ser	
	225					230					235					240	
20	Glu	Asn	His	Ser	Cys	Phe	Asp	Val	Val	Lys	Gln	Ile	Phe	Ala	Pro	Arg	
					245					250					255		
	Gln	Glu	Glu	Phe	His	Gln	Arg	Ala	Asn	Val	Thr	Phe	Thr	Leu	Ser	Lys	
				260					265						270		
25	Phe	His	Trp	Cys	Cys	His	His	His	Val	Gln	Val	Gln	Pro	Phe	Phe	Ser	
			275					280					285				
	Ser	Cys	Leu	Asn	Asp	Cys	Leu	Arg	His	Ala	Val	Thr	Val	Pro	Cys	Pro	
30		290					295					300					
	Val	Ile	Ser	Asn	Thr	Thr	Val	Pro	Lys	Pro	Val	Ala	Asp	Tyr	Ile	Pro	
	305					310					315					320	
35	Leu	Trp	Val	Tyr	Gly	Leu	Ile	Thr	Leu	Ile	Ala	Ile	Leu	Leu	Val	Gly	
					325					330					335		
	Ser	Val	Ile	Val	Leu	Ile	Ile	Cys	Met	Thr	Trp	Arg	Leu	Ser	Gly	Ala	
				340					345					350			
40	Asp	Gln	Glu	Lys	His	Gly	Asp	Asp	Ser	Lys	Ile	Asn	Gly	Ile	Leu	Pro	
			355				360						365				
	Val	Ala	Asp	Leu	Thr	Pro	Pro	Pro	Leu	Arg	Pro	Arg	Lys	Val	Trp	Ile	
45		370					375					380					
	Val	Tyr	Ser	Ala	Asp	His	Pro	Leu	Tyr	Val	Glu	Val	Val	Leu	Lys	Phe	
	385					390					395					400	
50	Ala	Gln	Phe	Leu	Ile	Thr	Ala	Cys	Gly	Thr	Glu	Val	Ala	Leu	Asp	Leu	
					405					410					415		
	Leu	Glu	Glu	Gln	Val	Ile	Ser	Glu	Val	Gly	Val	Met	Thr	Trp	Val	Ser	
				420					425					430			
55	Arg	Gln	Lys	Gln	Glu	Met	Val	Glu	Ser	Asn	Ser	Lys	Ile	Ile	Ile	Leu	
			435					440					445				
	Cys	Ser	Arg	Gly	Thr	Gln	Ala	Lys	Trp	Lys	Ala	Ile	Leu	Gly	Trp	Ala	
60		450					455					460					

	Glu	Pro	Ala	Val	Gln	Leu	Arg	Cys	Asp	His	Trp	Lys	Pro	Ala	Gly	Asp	465	470	475	480
5	Leu	Phe	Thr	Ala	Ala	Met	Asn	Met	Ile	Leu	Pro	Asp	Phe	Lys	Arg	Pro	485	490	495	
	Ala	Cys	Phe	Gly	Thr	Tyr	Val	Val	Cys	Tyr	Phe	Ser	Gly	Ile	Cys	Ser	500	505	510	
10	Glu	Arg	Asp	Val	Pro	Asp	Leu	Phe	Asn	Ile	Thr	Ser	Arg	Tyr	Pro	Leu	515	520	525	
15	Met	Asp	Arg	Phe	Glu	Glu	Val	Tyr	Phe	Arg	Ile	Gln	Asp	Leu	Glu	Met	530	535	540	
	Phe	Glu	Pro	Gly	Arg	Met	His	His	Val	Arg	Glu	Leu	Thr	Gly	Asp	Asn	545	550	555	560
20	Tyr	Leu	Gln	Ser	Pro	Ser	Gly	Arg	Gln	Leu	Lys	Glu	Ala	Val	Leu	Arg	565	570	575	
	Phe	Gln	Glu	Trp	Gln	Thr	Gln	Cys	Pro	Asp	Trp	Phe	Glu	Arg	Glu	Asn	580	585	590	
25	Leu	Cys	Leu	Ala	Asp	Gly	Gln	Asp	Leu	Pro	Ser	Leu	Asp	Glu	Glu	Val	595	600	605	
30	Phe	Glu	Asp	Pro	Leu	Leu	Pro	Pro	Gly	Gly	Gly	Ile	Val	Lys	Gln	Gln	610	615	620	
	Pro	Leu	Val	Arg	Glu	Leu	Pro	Ser	Asp	Gly	Cys	Leu	Val	Val	Asp	Val	625	630	635	640
35	Cys	Val	Ser	Glu	Glu	Glu	Ser	Arg	Met	Ala	Lys	Leu	Asp	Pro	Gln	Leu	645	650	655	
	Trp	Pro	Gln	Arg	Glu	Leu	Val	Ala	His	Thr	Leu	Gln	Ser	Met	Val	Leu	660	665	670	
40	Pro	Ala	Glu	Gln	Val	Pro	Ala	Ala	His	Val	Val	Glu	Pro	Leu	His	Leu	675	680	685	
45	Pro	Asp	Gly	Ser	Gly	Ala	Ala	Ala	Gln	Leu	Pro	Met	Thr	Glu	Asp	Ser	690	695	700	
	Glu	Ala	Cys	Pro	Leu	Leu	Gly	Val	Gln	Arg	Asn	Ser	Ile	Leu	Cys	Leu	705	710	715	720
50	Pro	Val	Asp	Ser	Asp	Asp	Leu	Pro	Leu	Cys	Ser	Thr	Pro	Met	Met	Ser	725	730	735	
	Pro	Asp	His	Leu	Gln	Gly	Asp	Ala	Arg	Glu	Gln	Leu	Glu	Ser	Leu	Met	740	745	750	
55	Leu	Ser	Val	Leu	Gln	Gln	Ser	Leu	Ser	Gly	Gln	Pro	Leu	Glu	Ser	Trp	755	760	765	
60	Pro	Arg	Pro	Glu	Val	Val	Leu	Glu	Gly	Cys	Thr	Pro	Ser	Glu	Glu	Glu	770	775	780	

Gln Arg Gln Ser Val Gln Ser Asp Gln Gly Tyr Ile Ser Arg Ser Ser
 785 790 795 800
 5 Pro Gln Pro Pro Glu Trp Leu Thr Glu Glu Glu Glu Leu Glu Leu Gly
 805 810 815
 Glu Pro Val Glu Ser Leu Ser Pro Glu Glu Leu Arg Ser Leu Arg Lys
 820 825 830
 10 Leu Gln Arg Gln Leu Phe Phe Trp Glu Leu Glu Lys Asn Pro Gly Trp
 835 840 845
 15 Asn Ser Leu Glu Pro Arg Arg Pro Thr Pro Glu Glu Gln Asn Pro Ser
 850 855 860
 *
 865

20

(2) INFORMATION FOR SEQ ID NO:3:

25 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 8 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: not relevant
 (D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: peptide

(vii) IMMEDIATE SOURCE:
 (B) CLONE: FLAG® peptide

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Asp Tyr Lys Asp Asp Asp Asp Lys
 1 5

40

(2) INFORMATION FOR SEQ ID NO:4:

45 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 213 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: not relevant
 (D) TOPOLOGY: linear

50 (ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
 (A) ORGANISM: Human

55 (vii) IMMEDIATE SOURCE:
 (B) CLONE: IgG1 Fc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

5 Arg Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
 1 5 10 15
 Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 20 25 30
 10 Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 35 40 45
 Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
 50 55 60
 15 Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
 65 70 75 80
 Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
 85 90 95
 20 Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
 100 105 110
 25 Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 115 120 125
 Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
 130 135 140
 30 Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 145 150 155 160
 Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 165 170 175
 35 Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 180 185 190
 40 Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
 195 200 205
 Cys Ser Val Met His
 210

45

(2) INFORMATION FOR SEQ ID NO:5:

50 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 14 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: not relevant
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: peptide
 55 (vii) IMMEDIATE SOURCE:
 (B) CLONE: Polylinker

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
 1 5 10

5

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

10

- (A) LENGTH: 498 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

20

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Murine CTLA-8

25

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 14..490

30

(ix) FEATURE:

- (A) NAME/KEY: sig_peptide
 (B) LOCATION: 14..88

35

(ix) FEATURE:

- (A) NAME/KEY: mat_peptide
 (B) LOCATION: 89..487

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

40

GTCGACCCCC ACC ATG TTC CAT GTT TCT TTT AGA TAT ATC TTT GGA ATT 49
 Met Phe His Val Ser Phe Arg Tyr Ile Phe Gly Ile
 -25 -20 -15

45

CCT CCA CTG ATC CTT GTT CTG CTG CCT GTC ACT AGT TCT GCG GTA CTC 97
 Pro Pro Leu Ile Leu Val Leu Leu Pro Val Thr Ser Ser Ala Val Leu
 -10 -5 1

50

ATC CCT CAA AGT TCA GCG TGT CCA AAC ACT GAG GCC AAG GAC TTC CTC 145
 Ile Pro Gln Ser Ser Ala Cys Pro Asn Thr Glu Ala Lys Asp Phe Leu
 5 10 15

CAG AAT GTG AAG GTC AAC CTC AAA GTC TTT AAC TCC CTT GGC GCA AAA 193
 Gln Asn Val Lys Val Asn Leu Lys Val Phe Asn Ser Leu Gly Ala Lys
 20 25 30 35

55

GTG AGC TCC AGA AGG CCC TCA GAC TAC CTC AAC CGT TCC ACG TCA CCC 241
 Val Ser Ser Arg Arg Pro Ser Asp Tyr Leu Asn Arg Ser Thr Ser Pro
 40 45 50

TGG ACT CTC CAC CGC AAT GAA GAC CCT GAT AGA TAT CCC TCT GTG ATC 289
 Trp Thr Leu His Arg Asn Glu Asp Pro Asp Arg Tyr Pro Ser Val Ile
 55 60 65
 5 TGG GAA GCT CAG TGC CGC CAC CAG CGC TGT GTC AAT GCG GAG GGA AAG 337
 Trp Glu Ala Gln Cys Arg His Gln Arg Cys Val Asn Ala Glu Gly Lys
 70 75 80
 10 CTG GAC CAC CAC ATG AAT TCT GTT CTC ATC CAG CAA GAG ATC CTG GTC 385
 Leu Asp His His Met Asn Ser Val Leu Ile Gln Gln Glu Ile Leu Val
 85 90 95
 15 CTG AAG AGG GAG CCT GAG AGC TGC CCC TTC ACT TTC AGG GTC GAG AAG 433
 Leu Lys Arg Glu Pro Glu Ser Cys Pro Phe Thr Phe Arg Val Glu Lys
 100 105 110 115
 20 ATG CTG GTG GGT GTG GGC TGC ACC TGC GTG GCC TCG ATT GTC CGC CAT 481
 Met Leu Val Gly Val Gly Cys Thr Cys Val Ala Ser Ile Val Arg His
 120 125 130
 GCG TCC TAA GCGGCCGC 498
 Ala Ser *

25

(2) INFORMATION FOR SEQ. ID. NO:7:

(i) SEQUENCE CHARACTERISTICS:

30

- (A) LENGTH: 159 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Met Phe His Val Ser Phe Arg Tyr Ile Phe Gly Ile Pro Pro Leu Ile
 -25 -20 -15 -10
 40 Leu Val Leu Leu Pro Val Thr Ser Ser Ala Val Leu Ile Pro Gln Ser
 -5 1 5
 Ser Ala Cys Pro Asn Thr Glu Ala Lys Asp Phe Leu Gln Asn Val Lys
 10 15 20
 45 Val Asn Leu Lys Val Phe Asn Ser Leu Gly Ala Lys Val Ser Ser Arg
 25 30 35
 50 Arg Pro Ser Asp Tyr Leu Asn Arg Ser Thr Ser Pro Trp Thr Leu His
 40 45 50 55
 Arg Asn Glu Asp Pro Asp Arg Tyr Pro Ser Val Ile Trp Glu Ala Gln
 60 65 70
 55 Cys Arg His Gln Arg Cys Val Asn Ala Glu Gly Lys Leu Asp His His
 75 80 85
 Met Asn Ser Val Leu Ile Gln Gln Glu Ile Leu Val Leu Lys Arg Glu
 90 95 100
 60

Pro Glu Ser Cys Pro Phe Thr Phe Arg Val Glu Lys Met Leu Val Gly
 105 110 115

5 Val Gly Cys Thr Cys Val Ala Ser Ile Val Arg His Ala Ser *
 120 125 130

(2) INFORMATION FOR SEQ ID NO:8:

10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 151 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: not relevant
 (D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

20 (iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Herpesvirus Saimiri
 (B) CLONE: ORF13

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

30 Met Thr Phe Arg Met Thr Ser Leu Val Leu Leu Leu Leu Ser Ile
 1 5 10 15
 Asp Cys Ile Val Lys Ser Glu Ile Thr Ser Ala Gln Thr Pro Arg Cys
 20 25 30
 35 Leu Ala Ala Asn Asn Ser Phe Pro Arg Ser Val Met Val Thr Leu Ser
 35 40 45
 Ile Arg Asn Trp Asn Thr Ser Ser Lys Arg Ala Ser Asp Tyr Tyr Asn
 50 55 60
 40 Arg Ser Thr Ser Pro Trp Thr Leu His Arg Asn Glu Asp Gln Asp Arg
 65 70 75 80
 Tyr Pro Ser Val Ile Trp Glu Ala Lys Cys Arg Tyr Leu Gly Cys Val
 45 85 90 95
 Asn Ala Asp Gly Asn Val Asp Tyr His Met Asn Ser Val Pro Ile Gln
 100 105 110
 50 Gln Glu Ile Leu Val Val Arg Lys Gly His Gln Pro Cys Pro Asn Ser
 115 120 125
 Phe Arg Leu Glu Lys Met Leu Val Thr Val Gly Cys Thr Cys Val Thr
 130 135 140
 55 Pro Ile Val His Asn Val Asp
 145 150

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 3223 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
 (A) ORGANISM: Human
 (B) CLONE: IL-17R

(ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 93..2693

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

25	GGGAGACCGG AATTCCGGGA AAAGAAAGCC TCAGAACGTT CGCTCGCTGC GTCCCCAGCC	60
30	GGGGCCGAGC CCTCCGCGAC GCCACCCGGG CC ATG GGG GCC GCA CGC AGC CCG Met Gly Ala Ala Arg Ser Pro 1 5	113
35	CCG TCC GCT GTC CCG GGG CCC CTG CTG GGG CTG CTC CTG CTG CTC CTG Pro Ser Ala Val Pro Gly Pro Leu Leu Gly Leu Leu Leu Leu Leu 10 15 20	161
40	GGC GTG CTG GCC CCG GGT GGC GCC TCC CTG CGA CTC CTG GAC CAC CGG Gly Val Leu Ala Pro Gly Gly Ala Ser Leu Arg Leu Leu Asp His Arg 25 30 35	209
45	GCG CTG GTC TGC TCC CAG CCG GGG CTA AAC TGC ACG GTC AAG AAT AGT Ala Leu Val Cys Ser Gln Pro Gly Leu Asn Cys Thr Val Lys Asn Ser 40 45 50 55	257
50	ACC TGC CTG GAT GAC AGC TGG ATT CAC CCT CGA AAC CTG ACC CCC TCC Thr Cys Leu Asp Asp Ser Trp Ile His Pro Arg Asn Leu Thr Pro Ser 60 65 70	305
55	TCC CCA AAG GAC CTG CAG ATC CAG CTG CAC TTT GCC CAC ACC CAA CAA Ser Pro Lys Asp Leu Gln Ile Gln Leu His Phe Ala His Thr Gln Gln 75 80 85	353
60	GGA GAC CTG TTC CCC GTG GCT CAC ATC GAA TGG ACA CTG CAG ACA GAC Gly Asp Leu Phe Pro Val Ala His Ile Glu Trp Thr Leu Gln Thr Asp 90 95 100	401
65	GCC AGC ATC CTG TAC CTC GAG GGT GCA GAG TTA TCT GTC CTG CAG CTG Ala Ser Ile Leu Tyr Leu Glu Gly Ala Glu Leu Ser Val Leu Gln Leu 105 110 115	449

	AAC	ACC	AAT	GAA	CGT	TTG	TGC	GTC	AGG	TTT	GAG	TTT	CTG	TCC	AAA	CTG	497
	Asn	Thr	Asn	Glu	Arg	Leu	Cys	Val	Arg	Phe	Glu	Phe	Leu	Ser	Lys	Leu	
	120					125					130					135	
5	AGG	CAT	CAC	CAC	AGG	CGG	TGG	CGT	TTT	ACC	TTC	AGC	CAC	TTT	GTG	GTT	545
	Arg	His	His	His	Arg	Arg	Trp	Arg	Phe	Thr	Phe	Ser	His	Phe	Val	Val	
					140					145					150		
10	GAC	CCT	GAC	CAG	GAA	TAT	GAG	GTG	ACC	GTT	CAC	CAC	CTG	CCC	AAG	CCC	593
	Asp	Pro	Asp	Gln	Glu	Tyr	Glu	Val	Thr	Val	His	His	Leu	Pro	Lys	Pro	
				155					160					165			
15	ATC	CCT	GAT	GGG	GAC	CCA	AAC	CAC	CAG	TCC	AAG	AAT	TTC	CTT	GTG	CCT	641
	Ile	Pro	Asp	Gly	Asp	Pro	Asn	His	Gln	Ser	Lys	Asn	Phe	Leu	Val	Pro	
			170					175					180				
20	GAC	TGT	GAG	CAC	GCC	AGG	ATG	AAG	GTA	ACC	ACG	CCA	TGC	ATG	AGC	TCA	689
	Asp	Cys	Glu	His	Ala	Arg	Met	Lys	Val	Thr	Thr	Pro	Cys	Met	Ser	Ser	
		185					190					195					
25	GGC	AGC	CTG	TGG	GAC	CCC	AAC	ATC	ACC	GTG	GAG	ACC	CTG	GAG	GCC	CAC	737
	Gly	Ser	Leu	Trp	Asp	Pro	Asn	Ile	Thr	Val	Glu	Thr	Leu	Glu	Ala	His	
	200					205					210				215		
30	CAG	CTG	CGT	GTG	AGC	TTC	ACC	CTG	TGG	AAC	GAA	TCT	ACC	CAT	TAC	CAG	785
	Gln	Leu	Arg	Val	Ser	Phe	Thr	Leu	Trp	Asn	Glu	Ser	Thr	His	Tyr	Gln	
					220					225					230		
35	ATC	CTG	CTG	ACC	AGT	TTT	CCG	CAC	ATG	GAG	AAC	CAC	AGT	TGC	TTT	GAG	833
	Ile	Leu	Leu	Thr	Ser	Phe	Pro	His	Met	Glu	Asn	His	Ser	Cys	Phe	Glu	
				235					240					245			
40	CAC	ATG	CAC	CAC	ATA	CCT	GCG	CCC	AGA	CCA	GAA	GAG	TTC	CAC	CAG	CGA	881
	His	Met	His	His	Ile	Pro	Ala	Pro	Arg	Pro	Glu	Glu	Phe	His	Gln	Arg	
			250					255					260				
45	TCC	AAC	GTC	ACA	CTC	ACT	CTA	CGC	AAC	CTT	AAA	GGG	TGC	TGT	CGC	CAC	929
	Ser	Asn	Val	Thr	Leu	Thr	Leu	Arg	Asn	Leu	Lys	Gly	Cys	Cys	Arg	His	
		265					270					275					
50	CAA	GTG	CAG	ATC	CAG	CCC	TTC	TTC	AGC	AGC	TGC	CTC	AAT	GAC	TGC	CTC	977
	Gln	Val	Gln	Ile	Gln	Pro	Phe	Phe	Ser	Ser	Cys	Leu	Asn	Asp	Cys	Leu	
	280					285					290				295		
55	AGA	CAC	TCC	GCG	ACT	GTT	TCC	TGC	CCA	GAA	ATG	CCA	GAC	ACT	CCA	GAA	1025
	Arg	His	Ser	Ala	Thr	Val	Ser	Cys	Pro	Glu	Met	Pro	Asp	Thr	Pro	Glu	
					300					305					310		
60	CCA	ATT	CCG	GAC	TAC	ATG	CCC	CTG	TGG	GTG	TAC	TGG	TTC	ATC	ACG	GGC	1073
	Pro	Ile	Pro	Asp	Tyr	Met	Pro	Leu	Trp	Val	Tyr	Trp	Phe	Ile	Thr	Gly	
				315					320					325			
65	ATC	TCC	ATC	CTG	CTG	GTG	GGC	TCC	GTC	ATC	CTG	CTC	ATC	GTC	TGC	ATG	1121
	Ile	Ser	Ile	Leu	Leu	Val	Gly	Ser	Val	Ile	Leu	Leu	Ile	Val	Cys	Met	
			330					335					340				
70	ACC	TGG	AGG	CTA	GCT	GGG	CCT	GGA	AGT	GAA	AAA	TAC	AGT	GAT	GAC	ACC	1169
	Thr	Trp	Arg	Leu	Ala	Gly	Pro	Gly	Ser	Glu	Lys	Tyr	Ser	Asp	Asp	Thr	
		345					350					355					

	AAA TAC ACC GAT GGC CTG CCT GCG GCT GAC CTG ATC CCC CCA CCG CTG	1217
	Lys Tyr Thr Asp Gly Leu Pro Ala Ala Asp Leu Ile Pro Pro Pro Leu	
	360 365 370 375	
5	AAG CCC AGG AAG GTC TGG ATC ATC TAC TCA GCC GAC CAC CCC CTC TAC	1265
	Lys Pro Arg Lys Val Trp Ile Ile Tyr Ser Ala Asp His Pro Leu Tyr	
	380 385 390	
10	GTG GAC GTG GTC CTG AAA TTC GCC CAG TTC CTG CTC ACC GCC TGC GGC	1313
	Val Asp Val Val Leu Lys Phe Ala Gln Phe Leu Leu Thr Ala Cys Gly	
	395 400 405	
15	ACG GAA GTG GCC CTG GAC CTG CTG GAA GAG CAG GCC ATC TCG GAG GCA	1361
	Thr Glu Val Ala Leu Asp Leu Leu Glu Glu Gln Ala Ile Ser Glu Ala	
	410 415 420	
20	GGA GTC ATG ACC TGG GTG GGC CGT CAG AAG CAG GAG ATG GTG GAG AGC	1409
	Gly Val Met Thr Trp Val Gly Arg Gln Lys Gln Glu Met Val Glu Ser	
	425 430 435	
25	AAC TCT AAG ATC ATC GTC CTG TGC TCC CGC GGC ACG CGC GCC AAG TGG	1457
	Asn Ser Lys Ile Ile Val Leu Cys Ser Arg Gly Thr Arg Ala Lys Trp	
	440 445 450 455	
30	CAG GCG CTC CTG GGC CGG GGG GCG CCT GTG CGG CTG CGC TGC GAC CAC	1505
	Gln Ala Leu Leu Gly Arg Gly Ala Pro Val Arg Leu Arg Cys Asp His	
	460 465 470	
35	GGA AAG CCC GTG GGG GAC CTG TTC ACT GCA GCC ATG AAC ATG ATC CTC	1553
	Gly Lys Pro Val Gly Asp Leu Phe Thr Ala Ala Met Asn Met Ile Leu	
	475 480 485	
40	CCG GAC TTC AAG AGG CCA GCC TGC TTC GGC ACC TAC GTA GTC TGC TAC	1601
	Pro Asp Phe Lys Arg Pro Ala Cys Phe Gly Thr Tyr Val Val Cys Tyr	
	490 495 500	
45	TTC AGC GAG GTC AGC TGT GAC GGC GAC GTC CCC GAC CTG TTC GGC GCG	1649
	Phe Ser Glu Val Ser Cys Asp Gly Asp Val Pro Asp Leu Phe Gly Ala	
	505 510 515	
50	GCG CCG CGG TAC CCG CTC ATG GAC AGG TTC GAG GAG GTG TAC TTC CGC	1697
	Ala Pro Arg Tyr Pro Leu Met Asp Arg Phe Glu Glu Val Tyr Phe Arg	
	520 525 530 535	
55	ATC CAG GAC CTG GAG ATG TTC CAG CCG GGC CGC ATG CAC CGC GTA GGG	1745
	Ile Gln Asp Leu Glu Met Phe Gln Pro Gly Arg Met His Arg Val Gly	
	540 545 550	
60	GAG CTG TCG GGG GAC AAC TAC CTG CGG AGC CCG GGC GGC AGG CAG CTC	1793
	Glu Leu Ser Gly Asp Asn Tyr Leu Arg Ser Pro Gly Gly Arg Gln Leu	
	555 560 565	
65	CGC GCC GCC CTG GAC AGG TTC CGG GAC TGG CAG GTC CGC TGT CCC GAC	1841
	Arg Ala Ala Leu Asp Arg Phe Arg Asp Trp Gln Val Arg Cys Pro Asp	
	570 575 580	
70	TGG TTC GAA TGT GAG AAC CTC TAC TCA GCA GAT GAC CAG GAT GCC CCG	1889
	Trp Phe Glu Cys Glu Asn Leu Tyr Ser Ala Asp Asp Gln Asp Ala Pro	
	585 590 595	

	TCC	CTG	GAC	GAA	GAG	GTG	TTT	GAG	GAG	CCA	CTG	CTG	CCT	CCG	GGA	ACC	1937
	Ser	Leu	Asp	Glu	Glu	Val	Phe	Glu	Glu	Pro	Leu	Leu	Pro	Pro	Gly	Thr	
	600					605					610					615	
5	GGC	ATC	GTG	AAG	CGG	GCG	CCC	CTG	GTG	CGC	GAG	CCT	GGC	TCC	CAG	GCC	1985
	Gly	Ile	Val	Lys	Arg	Ala	Pro	Leu	Val	Arg	Glu	Pro	Gly	Ser	Gln	Ala	
					620					625					630		
10	TGC	CTG	GCC	ATA	GAC	CCG	CTG	GTC	GGG	GAG	GAA	GGA	GGA	GCA	GCA	GTG	2033
	Cys	Leu	Ala	Ile	Asp	Pro	Leu	Val	Gly	Glu	Glu	Gly	Gly	Ala	Ala	Val	
				635					640					645			
15	GCA	AAG	CTG	GAA	CCT	CAC	CTG	CAG	CCC	CGG	GGT	CAG	CCA	GCG	CCG	CAG	2081
	Ala	Lys	Leu	Glu	Pro	His	Leu	Gln	Pro	Arg	Gly	Gln	Pro	Ala	Pro	Gln	
			650					655					660				
20	CCC	CTC	CAC	ACC	CTG	GTG	CTC	GCC	GCA	GAG	GAG	GGG	GCC	CTG	GTG	GCC	2129
	Pro	Leu	His	Thr	Leu	Val	Leu	Ala	Ala	Glu	Glu	Gly	Ala	Leu	Val	Ala	
		665					670					675					
	GCG	GTG	GAG	CCT	GGG	CCC	CTG	GCT	GAC	GGT	GCC	GCA	GTC	CGG	CTG	GCA	2177
	Ala	Val	Glu	Pro	Gly	Pro	Leu	Ala	Asp	Gly	Ala	Ala	Val	Arg	Leu	Ala	
	680					685					690					695	
25	CTG	GCG	GGG	GAG	GGC	GAG	GCC	TGC	CCG	CTG	CTG	GGC	AGC	CCG	GGC	GCT	2225
	Leu	Ala	Gly	Glu	Gly	Glu	Ala	Cys	Pro	Leu	Leu	Gly	Ser	Pro	Gly	Ala	
					700					705					710		
30	GGG	CGA	AAT	AGC	GTC	CTC	TTC	CTC	CCC	GTG	GAC	CCC	GAG	GAC	TCG	CCC	2273
	Gly	Arg	Asn	Ser	Val	Leu	Phe	Leu	Pro	Val	Asp	Pro	Glu	Asp	Ser	Pro	
				715					720					725			
35	CTT	GGC	AGC	AGC	ACC	CCC	ATG	GCG	TCT	CCT	GAC	CTC	CTT	CCA	GAG	GAC	2321
	Leu	Gly	Ser	Ser	Thr	Pro	Met	Ala	Ser	Pro	Asp	Leu	Leu	Pro	Glu	Asp	
			730					735					740				
40	GTG	AGG	GAG	CAC	CTC	GAA	GGC	TTG	ATG	CTC	TCG	CTC	TTC	GAG	CAG	AGT	2369
	Val	Arg	Glu	His	Leu	Glu	Gly	Leu	Met	Leu	Ser	Leu	Phe	Glu	Gln	Ser	
		745					750					755					
	CTG	AGC	TGC	CAG	GCC	CAG	GGG	GGC	TGC	AGT	AGA	CCC	GCC	ATG	GTC	CTC	2417
	Leu	Ser	Cys	Gln	Ala	Gln	Gly	Gly	Cys	Ser	Arg	Pro	Ala	Met	Val	Leu	
	760					765					770					775	
45	ACA	GAC	CCA	CAC	ACG	CCC	TAC	GAG	GAG	GAG	CAG	CGG	CAG	TCA	GTG	CAG	2465
	Thr	Asp	Pro	His	Thr	Pro	Tyr	Glu	Glu	Glu	Gln	Arg	Gln	Ser	Val	Gln	
					780					785					790		
50	TCT	GAC	CAG	GGC	TAC	ATC	TCC	AGG	AGC	TCC	CCG	CAG	CCC	CCC	GAG	GGA	2513
	Ser	Asp	Gln	Gly	Tyr	Ile	Ser	Arg	Ser	Ser	Pro	Gln	Pro	Pro	Glu	Gly	
				795					800					805			
55	CTC	ACG	GAA	ATG	GAG	GAA	GAG	GAG	GAA	GAG	GAG	CAG	GAC	CCA	GGG	AAG	2561
	Leu	Thr	Glu	Met	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Gln	Asp	Pro	Gly	Lys	
			810					815					820				
60	CCG	GCC	CTG	CCA	CTC	TCT	CCC	GAG	GAC	CTG	GAG	AGC	CTG	AGG	AGC	CTC	2609
	Pro	Ala	Leu	Pro	Leu	Ser	Pro	Glu	Asp	Leu	Glu	Ser	Leu	Arg	Ser	Leu	
		825					830					835					

	CAG CGG CAG CTG CTT TTC CGC CAG CTG CAG AAG AAC TCG GGC TGG GAC	2657
	Gln Arg Gln Leu Leu Phe Arg Gln Leu Gln Lys Asn Ser Gly Trp Asp	
	840 845 850 855	
5	ACG ATG GGG TCA GAG TCA GAG GGG CCC AGT GCA TGA GGGCGGCTCC	2703
	Thr Met Gly Ser Glu Ser Glu Gly Pro Ser Ala *	
	860 865	
10	CCAGGGACCG CCCAGATCCC AGCTTTGAGA GAGGAGTGTG TGTGCACGTA TTCATCTGTG	2763
	TGTACATGTC TGCATGTGTA TATGTTTCGTG TGTGAAATGT AGGCTTTAAA ATGTAAATGT	2823
	CTGGATTTTA ATCCCAGGCA TCCCTCCTAA CTTTTCTTTG TGCAGCGGTC TGGTTATCGT	2883
15	CTATCCCCAG GGAATCCAC ACAGCCCGCT CCCAGGAGCT AATGGTAGAG CGTCCTTGAG	2943
	GCTCCATTAT TCGTTCATTTC AGCATTTATT GTGCACCTAC TATGTGGCGG GCATTTGGGA	3003
20	TACCAAGATA AATTGCATGC GGCATGGCCC CAGCCATGAA GGAACCTAAC CGCTAGTGCC	3063
	GAGGACACGT TAAACGAACA GGATGGGCCG GGCACGGTGG CTCACGCCTG TAATCCCAGC	3123
	ACACTGGGAG GCCGAGGCAG GTGGATCACT CTGAGGTCAG GAGTTTGAGC CAGCCTGGCC	3183
25	AACATGGTGA AACCCCGGAA TTCGAGCTCG GTACCCGGGG	3223

(2) INFORMATION FOR SEQ ID NO:10:

30 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 867 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

40	Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu	1 5 10 15
	Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser	20 25 30
45	Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu	35 40 45
	Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His	50 55 60
50	Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu	65 70 75 80
55	His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile	85 90 95
	Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala	100 105 110

	Glu	Leu	Ser	Val	Leu	Gln	Leu	Asn	Thr	Asn	Glu	Arg	Leu	Cys	Val	Arg	
			115					120					125				
5	Phe	Glu	Phe	Leu	Ser	Lys	Leu	Arg	His	His	His	Arg	Arg	Trp	Arg	Phe	
		130					135					140					
	Thr	Phe	Ser	His	Phe	Val	Val	Asp	Pro	Asp	Gln	Glu	Tyr	Glu	Val	Thr	
	145					150					155					160	
10	Val	His	His	Leu	Pro	Lys	Pro	Ile	Pro	Asp	Gly	Asp	Pro	Asn	His	Gln	
					165					170					175		
	Ser	Lys	Asn	Phe	Leu	Val	Pro	Asp	Cys	Glu	His	Ala	Arg	Met	Lys	Val	
15				180					185					190			
	Thr	Thr	Pro	Cys	Met	Ser	Ser	Gly	Ser	Leu	Trp	Asp	Pro	Asn	Ile	Thr	
			195					200					205				
20	Val	Glu	Thr	Leu	Glu	Ala	His	Gln	Leu	Arg	Val	Ser	Phe	Thr	Leu	Trp	
		210					215					220					
	Asn	Glu	Ser	Thr	His	Tyr	Gln	Ile	Leu	Leu	Thr	Ser	Phe	Pro	His	Met	
	225					230					235					240	
25	Glu	Asn	His	Ser	Cys	Phe	Glu	His	Met	His	His	Ile	Pro	Ala	Pro	Arg	
					245					250					255		
	Pro	Glu	Glu	Phe	His	Gln	Arg	Ser	Asn	Val	Thr	Leu	Thr	Leu	Arg	Asn	
30				260					265					270			
	Leu	Lys	Gly	Cys	Cys	Arg	His	Gln	Val	Gln	Ile	Gln	Pro	Phe	Phe	Ser	
			275					280					285				
	Ser	Cys	Leu	Asn	Asp	Cys	Leu	Arg	His	Ser	Ala	Thr	Val	Ser	Cys	Pro	
35			290				295					300					
	Glu	Met	Pro	Asp	Thr	Pro	Glu	Pro	Ile	Pro	Asp	Tyr	Met	Pro	Leu	Trp	
	305					310					315					320	
40	Val	Tyr	Trp	Phe	Ile	Thr	Gly	Ile	Ser	Ile	Leu	Leu	Val	Gly	Ser	Val	
				325						330					335		
	Ile	Leu	Leu	Ile	Val	Cys	Met	Thr	Trp	Arg	Leu	Ala	Gly	Pro	Gly	Ser	
45				340					345					350			
	Glu	Lys	Tyr	Ser	Asp	Asp	Thr	Lys	Tyr	Thr	Asp	Gly	Leu	Pro	Ala	Ala	
			355					360					365				
50	Asp	Leu	Ile	Pro	Pro	Pro	Leu	Lys	Pro	Arg	Lys	Val	Trp	Ile	Ile	Tyr	
		370					375					380					
	Ser	Ala	Asp	His	Pro	Leu	Tyr	Val	Asp	Val	Val	Leu	Lys	Phe	Ala	Gln	
		385				390					395					400	
55	Phe	Leu	Leu	Thr	Ala	Cys	Gly	Thr	Glu	Val	Ala	Leu	Asp	Leu	Leu	Glu	
					405					410					415		
	Glu	Gln	Ala	Ile	Ser	Glu	Ala	Gly	Val	Met	Thr	Trp	Val	Gly	Arg	Gln	
60				420					425					430			

Lys Gln Glu Met Val Glu Ser Asn Ser Lys Ile Ile Val Leu Cys Ser
 435 440 445
 5 Arg Gly Thr Arg Ala Lys Trp Gln Ala Leu Leu Gly Arg Gly Ala Pro
 450 455 460
 Val Arg Leu Arg Cys Asp His Gly Lys Pro Val Gly Asp Leu Phe Thr
 465 470 475 480
 10 Ala Ala Met Asn Met Ile Leu Pro Asp Phe Lys Arg Pro Ala Cys Phe
 485 490 495
 Gly Thr Tyr Val Val Cys Tyr Phe Ser Glu Val Ser Cys Asp Gly Asp
 500 505 510
 15 Val Pro Asp Leu Phe Gly Ala Ala Pro Arg Tyr Pro Leu Met Asp Arg
 515 520 525
 Phe Glu Glu Val Tyr Phe Arg Ile Gln Asp Leu Glu Met Phe Gln Pro
 530 535 540
 Gly Arg Met His Arg Val Gly Glu Leu Ser Gly Asp Asn Tyr Leu Arg
 545 550 555 560
 25 Ser Pro Gly Gly Arg Gln Leu Arg Ala Ala Leu Asp Arg Phe Arg Asp
 565 570 575
 Trp Gln Val Arg Cys Pro Asp Trp Phe Glu Cys Glu Asn Leu Tyr Ser
 580 585 590
 30 Ala Asp Asp Gln Asp Ala Pro Ser Leu Asp Glu Glu Val Phe Glu Glu
 595 600 605
 Pro Leu Leu Pro Pro Gly Thr Gly Ile Val Lys Arg Ala Pro Leu Val
 610 615 620
 Arg Glu Pro Gly Ser Gln Ala Cys Leu Ala Ile Asp Pro Leu Val Gly
 625 630 635 640
 40 Glu Glu Gly Gly Ala Ala Val Ala Lys Leu Glu Pro His Leu Gln Pro
 645 650 655
 Arg Gly Gln Pro Ala Pro Gln Pro Leu His Thr Leu Val Leu Ala Ala
 660 665 670
 45 Glu Glu Gly Ala Leu Val Ala Ala Val Glu Pro Gly Pro Leu Ala Asp
 675 680 685
 Gly Ala Ala Val Arg Leu Ala Leu Ala Gly Glu Gly Glu Ala Cys Pro
 690 695 700
 50 Leu Leu Gly Ser Pro Gly Ala Gly Arg Asn Ser Val Leu Phe Leu Pro
 705 710 715 720
 55 Val Asp Pro Glu Asp Ser Pro Leu Gly Ser Ser Thr Pro Met Ala Ser
 725 730 735
 Pro Asp Leu Leu Pro Glu Asp Val Arg Glu His Leu Glu Gly Leu Met
 740 745 750
 60

Leu Ser Leu Phe Glu Gln Ser Leu Ser Cys Gln Ala Gln Gly Gly Cys
755 760 765

5 Ser Arg Pro Ala Met Val Leu Thr Asp Pro His Thr Pro Tyr Glu Glu
770 775 780

Glu Gln Arg Gln Ser Val Gln Ser Asp Gln Gly Tyr Ile Ser Arg Ser
785 790 795 800

10 Ser Pro Gln Pro Pro Glu Gly Leu Thr Glu Met Glu Glu Glu Glu Glu
805 810 815

Glu Glu Gln Asp Pro Gly Lys Pro Ala Leu Pro Leu Ser Pro Glu Asp
820 825 830

15 Leu Glu Ser Leu Arg Ser Leu Gln Arg Gln Leu Leu Phe Arg Gln Leu
835 840 845

20 Gln Lys Asn Ser Gly Trp Asp Thr Met Gly Ser Glu Ser Glu Gly Pro
850 855 860

Ser Ala *
865

25

CLAIMS

We claim:

1. An isolated DNA selected from the group consisting of:
 - 5 (a) a DNA encoding a protein having an amino acid sequence of amino acids 1 through 322 of SEQ ID NO.: 2;
 - (b) a DNA encoding a protein having an amino acid sequence of amino acids 1 through 320 of SEQ ID NO.: 10; and
 - (c) DNA molecules capable of hybridization to the DNA of (a) or (b) under
10 stringent conditions, and which encode IL-17R that bind IL-17; and
 - (d) DNA molecules encoding fragments of proteins encoded by the DNA of (a), (b), or (c), which fragments bind IL-17.
- 15 2. An isolated oligonucleotide that is a fragment of a DNA according to claim 1, selected from the group consisting of oligonucleotides of at least about 17 nucleotides in length, oligonucleotides of at least about 25 nucleotides in length, and oligonucleotides of at least about 30 nucleotides in length.
- 20 3. An isolated DNA selected from the group consisting of:
 - (a) a DNA encoding a protein having an amino acid sequence of amino acids 1 through 322 of SEQ ID NO.: 2;
 - (b) a DNA encoding a protein having an amino acid sequence of amino acids 1 through 320 of SEQ ID NO.: 10;
 - (c) DNA molecules encoding proteins that are at least about 70% identical in
25 amino acid sequence to the proteins of (a) or (b), and that bind IL-17; and
 - (d) DNA molecules encoding fragments of proteins encoded by the DNA of (a), (b), or (c), which fragments bind IL-17.
- 30 4. A recombinant expression vector comprising a DNA sequence according to claim 1.
5. A recombinant expression vector according to claim 4 that expresses a soluble IL-17R.
- 35 6. A recombinant expression vector comprising a DNA sequence according to claim 3.
7. A host cell transformed or transfected with an expression vector according to claim 4.

8. A host cell transformed or transfected with an expression vector according to claim 5.

5 9. A host cell transformed or transfected with an expression vector according to claim 6.

10 10. A process for preparing an IL-17R protein, comprising culturing a host cell according to claim 7 under conditions promoting expression and recovering the IL-17R.

11. A process for preparing an IL-17R protein, comprising culturing a host cell according to claim 8 under conditions promoting expression and recovering the IL-17R.

15 12. A process for preparing an IL-17R protein, comprising culturing a host cell according to claim 9 under conditions promoting expression and recovering the IL-17R.

13. An isolated and purified Interleukin-17 receptor (IL-17R) protein that binds IL-17, selected from the group consisting of

20 (a) a protein having an amino acid sequence of amino acids 1 through 322 of SEQ ID NO.: 2;

(b) a protein having an amino acid sequence of amino acids 1 through 320 of SEQ ID NO.: 10;

(c) proteins encoded by DNA molecules capable of hybridization to DNA's encoding the proteins of (a) or (b) under stringent conditions, and which bind IL-17; and

25 (d) fragments of the proteins of (a), (b), or (c), that bind IL-17.

14. An isolated and purified IL-17R protein, selected from the group consisting of:

(a) a protein having an amino acid sequence of amino acids 1 through 322 of SEQ ID NO.: 2;

30 (b) a protein having an amino acid sequence of amino acids 1 through 320 of SEQ ID NO.: 10;

(c) a protein having an amino acid sequence that is at least about 70% identical to the amino acid sequences of the proteins of (a) or (b), and that binds IL-17; and

(d) fragments of the proteins of (a), (b), or (c), that bind IL-17.

35

15. An isolated and purified IL-17R according to claim 14, consisting essentially of soluble IL-17R.

16. A composition comprising an IL-17R protein according to claim 13, and a suitable diluent or carrier.
- 5 17. A method for regulating an immune or inflammatory response in a mammal, comprising administering an effective amount of a composition according to claim 16.
- 10 18. An assay kit for detection of IL-17, IL-17R, the interaction of IL-17 and IL-17R, or antagonists or mimetics of the interaction, comprising a protein composition according to claim 16, and a detecting reagent.
19. An antibody immunoreactive with IL-17R.
20. The antibody of claim 19 which is a monoclonal antibody.
- 15 21. A method for suppressing rejection of a grafted organ or grafted tissue in a graft recipient, comprising administering an effective amount of a composition according to claim 16 to the recipient.
- 20 22. A method for suppressing rejection of a grafted organ or grafted tissue in a graft recipient, comprising transfecting the organ or tissue to be transplanted with a DNA encoding a soluble IL-17R according to claim 1, and engrafting the organ or tissue in the recipient.
23. The method according to claim 22, further comprising administering a composition according to claim 16 to the recipient.
- 25 24. The use of an IL-17R protein according to claim 13 or 14 for preparation of a composition for suppressing rejection of a grafted organ or grafted tissue in a graft recipient.
25. The use of a DNA encoding a soluble IL-17R according to claim 1 or 3 for preparation of a composition for suppressing rejection of a grafted organ or grafted tissue in a graft recipient.
- 30 26. The use of a DNA encoding a soluble IL-17R according to claim 1 or 3 and an IL-17R protein according to claim 13 or 14, for preparation of a composition or compositions for separate, simultaneous or sequential administration for suppressing rejection of a grafted organ or grafted tissue in a graft recipient.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/04018

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12N15/85 C12N5/10 C07K14/715 A61K38/17
G01N33/68 C07K16/28 A61K48/00 //C12N15/62, C07K19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCIENCE, vol. 248, no. 4950, 11 May 1990, WASHINGTON, DC, USA, pages 739-742, XP002010936 W. FANSLOW ET AL.: "Regulation of alloreactivity in vivo by a soluble form of the interleukin-1 receptor." see abstract	13-17, 21,24
A	THE JOURNAL OF IMMUNOLOGY, vol. 147, no. 2, 15 July 1991, BALTIMORE, MD, USA, pages 535-540, XP002010937 W. FANSLOW ET AL.: "Regulation of alloreactivity in vivo by IL-4 and the soluble IL-4 receptor." see abstract	13-17, 21,24

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

14 August 1996

Date of mailing of the international search report

22.08.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Nooij, F

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/04018

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>IMMUNITY, vol. 3, no. 6, December 1995, USA, pages 811-821, XP000578349 Z. YAO ET AL.: "Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor." see the whole document</p> <p style="text-align: center;">---</p>	1-19
P,X	<p>WO,A,95 18826 (SCHERING CORP. & INSERM) 13 July 1995 see claims 14-17.</p> <p style="text-align: center;">-----</p>	13-15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/04018

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17, 21-23
because they relate to subject matter not required to be searched by this Authority, namely:
Although these claims are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Information on patent family members

PCT/US 96/04018

WO-A-9518826

13-07-95

AU-B- 1520895

01-08-95

